Slobodan M. Janković

A HANDBOOK OF PHARMACOLOGY AND TOXICOLOGY

- seventh, amended and supplemented edition -

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САДРЖАЈ

PREFACE

This time, the reader has before him the seventh edition of the "Handbook of Pharmacology and Toxicology". Like the previous six editions, this one has been supplemented with new knowledge that has appeared in the meantime. However, in this edition, I do not give up on the concept of the minimum of facts that future general practitioners need in their daily work. The most important facts that every general practitioner must know are written in the largest font and bold letters, so that the student can concentrate on what constitutes the core of the science of drugs and poisons.

The book should be read in its entirety, from beginning to end, and then, during the study, return to individual parts in order to better remember the relevant facts. The goal when studying pharmacology and toxicology should not be to memorize as many drug names as possible, but to consider all the therapeutic options available to us. Before using any drug on a patient, the doctor is obliged to check the detailed information on the method of its administration in the monograph of that drug, i.e. the summary of the characteristics of the drug, which are published together for all drugs in the appropriate compendiums or on the websites of drug agencies. Therefore, from this book one should understand the basic principles, which will later enable the use of detailed information in practice.

The manual is a book with a dual purpose: it should enable students to more easily master the most important facts, and to the doctors it will be a useful reminder for orientation in the forest of data on drugs they are faced with.

prof. dr Slobodan M. Janković

WARNING!
All drug doses listed in the text refer to an adult weighing approximately 70 kilograms, unless otherwise stated. The author has made every effort to ensure that all the facts presented in this book are accurate, but he disclaims any responsibility for the consequences arising from the use of these facts for any purpose. Knowledge in pharmacology changes and is supplemented at a rapid pace, so that by the time this book goes to press, some of the facts in this book will be outdated; therefore, the most up-to-date knowledge found in scientific journals and regularly updated summaries of drug characteristics must always be used in the treatment of patients.

GENERAL PHARMACOLOGY

PHARMACODYNAMICS

Pharmacology is the science that studies the interactions of chemical substances with a living organism. It consists of two major parts: pharmacodynamics and pharmacokinetics. Pharmacodynamics studies the effects of a drug on the organism, and pharmacokinetics the fate of the drug in the organism (absorption, distribution, metabolism and excretion). Toxicology is the science of toxic substances, their effects on the organism and the treatment of poisoned people. Pharmacotherapy is the applied science of the rational use of drugs in therapy.

A drug is any substance that, when introduced into the organism, leads to an improvement or cure of a disease, prevents it or helps in the diagnosis of a disease. A poison is a substance that, when introduced into the organism in a relatively small dose, causes its damage or death. The boundary between a poison and a drug is sometimes very unclear: the same substance can be both a drug and a poison, depending on the dose used. For example, cardiotonic glycosides are very effective drugs in therapeutic doses that can help a lot with heart failure; but if their dose is increased only a few times, they can lead to heart rhythm disorders and even death. Even ordinary water can be a poison: cases of psychogenic polydipsia have been described, when people drank 6-7 liters of water in a few hours, after which they developed pulmonary and cerebral edema, with a fatal outcome. The unclear boundary between medicine and poison was noticed by Paracelsus, a 16th century physician, who said: "All substances are poisons, there is not one that is not. It depends only on the dose whether something will be a medicine or a poison".

The largest number of drugs work by binding to a specific site in the body, which we call a receptor. A receptor is always a macromolecule, most often a protein, to which a natural, endogenous substance binds under physiological conditions, causing changes in the shape of the receptor (so-called conformational changes). Such a substance is called an endogenous ligand. Changes in the shape of the receptor caused by the binding of an endogenous ligand most often initiate a series of reactions in the cells on or in which the receptor is located, which result in a certain effect of the endogenous substance. The receptor has actually switched to an activated state by the binding of the ligand. Drugs that bind to receptors are similar in chemical structure to endogenous ligands. If a drug causes changes in the shape of the receptor similar to the changes that occur after the binding of an endogenous ligand (i.e. the receptor switches to an active state), such a drug is called an agonist. If, however, a drug does not cause any shape changes after binding to the receptor (i.e., the receptor remains in an inactive state), but only interferes with the binding (and thus the action) of the endogenous ligand, such a drug is called an antagonist. For example, the endogenous ligand of muscarinic receptors in the parasympathetic nervous system is acetylcholine; it converts the muscarinic receptor into an active state, and causes certain effects. The alkaloid muscarine, the active principle of poisonous mushrooms from the genus Inocybe, has the same effect as acetylcholine, so we call it an agonist of muscarinic receptors. On the other hand, atropine, the active principle of nightshade, binds to muscarinic receptors and keeps them in an inactive state, so it is called an antagonist of muscarinic receptors.

Agonists and antagonists can bind to the same site on the receptor as the endogenous ligand, and then we speak of **orthosteric** binding and the eventual interaction between the endogenous ligand, agonist, or antagonist. If the drug binds to a different site on the receptor than the one to which the endogenous ligand binds, and if the binding leads to an increase or decrease in the effect of the endogenous ligand, then we speak of **allosteric** binding and the modification of the effect of the endogenous ligand.

In terms of activity, receptors can be classified into two types: receptors that are inactive until an endogenous ligand binds to them, and receptors that are active when no endogenous ligand is bound to them.

Some receptors are in an activated state even without an endogenous ligand, i.e. they are constitutively active. An endogenous ligand inactivates such receptors, i.e. causes a conformational change in them that interrupts their

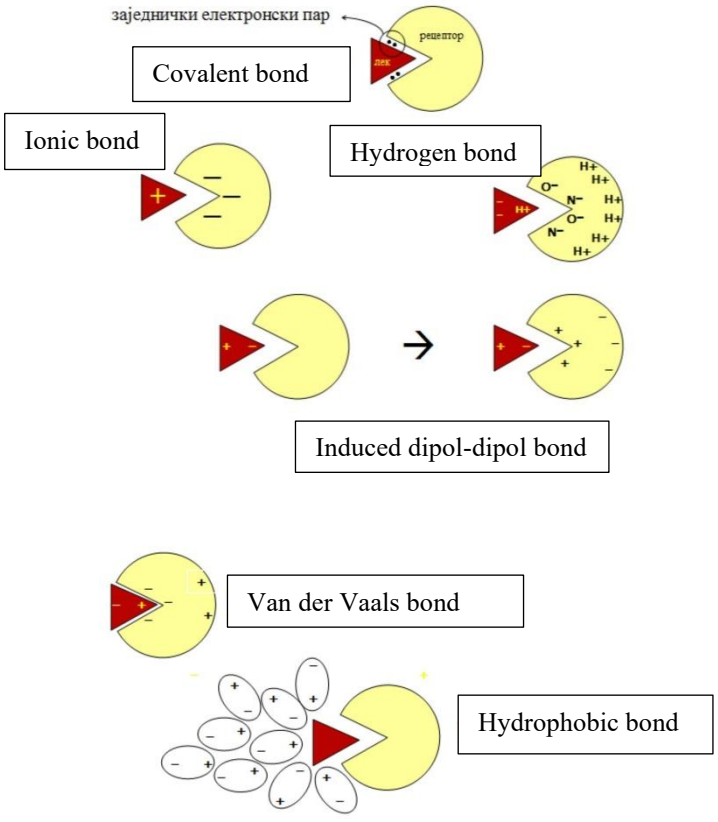
activity. Drugs that bind to such receptors, and which, like endogenous ligands, cause a conformational change that converts the receptor into an inactive state, are called **inverse agonists**. An example of a constitutively active receptor is the melano-stimulating hormone receptor, type MC4, which reduces hunger. Their endogenous ligand, the so-called agouti-related peptide, acts as an inverse agonist, i.e. converts the receptor into an inactive state, thereby increasing hunger.

There is a small number of drugs that do not act by the receptor mechanism, but in other ways. For example, the osmotic diuretic mannitol promotes water excretion from the body by creating a high osmolarity of the primary urine and thus preventing water reabsorption. So do antacids, drugs that, as weak bases, directly neutralize hydrochloric acid in the stomach after oral administration. However, receptor binding remains by far the most widespread mechanism of drug action.

BONDS BETWEEN A DRUG AND RECEPTOR

A drug can bind to a receptor in different ways (Figure 1). A less common way is covalent binding of a drug to a receptor, when two atoms share a pair of electrons. Covalent bonds are extremely strong, rich in energy, so they are difficult to break. Therefore, the receptor is most often irreversibly changed, and the effect of the drug ceases only when new receptors are synthesized. Alkylating cytostatics work in this way.

Figure 1. Bonds between a drug and receptor.



In the binding of a drug to a receptor, multiple types of bonds often play a role. The drug is usually attracted to the receptor by ionic bonds, which act at the greatest distance. When it approaches the receptor, if its three-dimensional structure matches the three-dimensional structure of the receptor binding site, the drug comes close enough to establish van der Waals bonds, and the receptor is activated or inactivated.

Finally, a drug and a receptor that are very hydrophobic can come into contact because the water dipoles push them apart. We call this effect **hydrophobic interaction**.

OPTICAL ISOMERIA

If a drug has a carbon atom in its molecule that is bonded to 4 different groups, then it can exist in two isomeric forms that differ from each other in terms of chemical structure only in the spatial arrangement of the groups bonded to that so-called asymmetric carbon atom (Figure 2). However, these two forms differ greatly in their pharmacological action. Only one of them will spatially correspond to the binding site on the receptor, i.e., only one of them will bind to the receptor. These isomers are called stereo or optical isomers because they have been shown to rotate the plane of polarized light in opposite directions. One of the isomers is designated as the L-isomer, and the other as the D-isomer. Most drugs that possess optical isomerism can only be obtained as an equimolar mixture of both isomers. Such mixtures are called racemates. Their application is sometimes fraught with difficulties because the isomers can have completely opposite effects.

A classic example of optical isomers is the antimalarial quinine and the antiarrhythmic quinidine. These two compounds have the same structural formula, but differ in the spatial arrangement of the groups attached to the two asymmetric carbon atoms, i.e., the two chiral centers. Since the differences exist at the two chiral centers, they are called diastereoisomers.

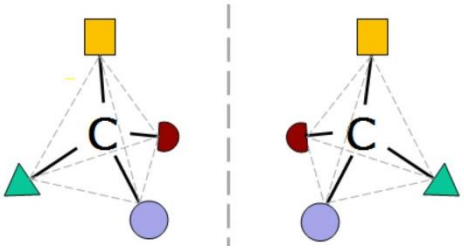


Figure 2. Optical isomeria.

INTERACTIONS BETWEEN DRUG AND RECEPTOR

The binding of a drug to a receptor is generally a reversible reaction that is subject to the law of active masses. Namely, the drug and the receptor always tend to reach an equilibrium state in which the rate of drug binding to the receptor is equal to the rate of degradation of the drug-receptor complex.

The body's response to a drug can be **gradual** (by increasing the dose of the drug, we get an increasingly greater response, until a maximum response or "plateau" is reached) or according to the "**all or nothing**" principle. An example of a gradual response is an increasingly greater decrease in blood pressure, when we give increasing doses of an antihypertensive. An example of a response according to the "all or nothing" principle is the effect of antiepileptic drugs: the drug either prevents the onset of seizures, or it does not prevent them.

It is customary to present the drug concentration on a logarithmic scale in a graphic representation of a gradual (graded) response. This theoretical dependence of the response of the body or some of its parts on the concentration of free drug near the receptor has been confirmed experimentally many times. With a logarithmic concentration scale, we obtain sigmoid response curves, which we call dose-response curves.

If we compare the dose-response curves for several drugs in the same experimental system (e.g., in an isolated organ), we can compare the affinity of these drugs for the receptor they act on and their intrinsic activity. The affinity of a drug for a receptor is a measure of the probability that the drug will bind to the receptor. The affinity is higher the further the dose-response curve is shifted to the left, i.e., if the effect can be achieved with smaller doses of the drug. On the other hand, the mere binding of a drug to a receptor does not mean that it will cause changes in the receptor, and thus in the cell, i.e., it does not mean that the drug will also have intrinsic activity. We measure this by the magnitude of the maximum effect that can be achieved with a given drug. In the following figure, drug A has a higher affinity for receptors than drug B, but the intrinsic activity of drug B is significantly higher. If we measure the effects of a drug in vivo, on the whole organism, then instead of affinity we talk about the strength of the drug's effect, and instead of intrinsic activity, we talk about the efficacy of the drug. These quantities are not uniquely related, because when drugs are administered to the whole organism, the absorption, metabolism and excretion of the drug also affect the final effect of the drug. In practice, the efficacy of the drug is of the greatest importance because the success of the treatment of patients depends on it the most. Very rarely is the strength of the effect of a drug so low that it makes the practical application of the drug difficult.

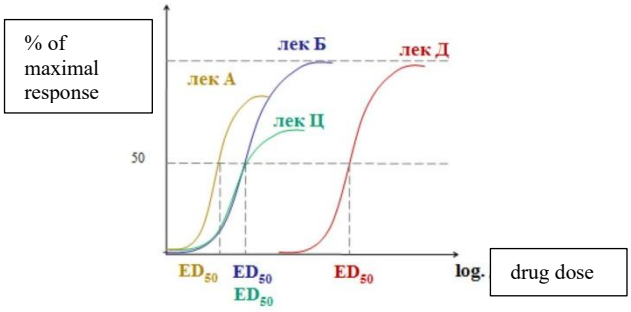


Figure 3. Concentration-response curves for drugs that act on the same receptor, but differ in affinity and intrinsic activity.

The effect of drugs that act on the principle of "all or nothing" can also be shown graphically, using the so-called quantum dose-response curve. If we plot the logarithm of the drug dose on the x-axis, and the percentage of patients who respond to a certain dose on the y-axis, we will get a sigmoid curve. From such a curve we can determine the dose of the drug at which 50% of patients will respond to the drug. Such a dose is called the "effective dose 50%" (ED50). Sometimes the body's response to a

drug is of the "either...or..." type ("**all or nothing**"), e.g., the drug either stops or does not stop a convulsive seizure. In that case, we cannot speak of 50% of the desired effect, but of the number (percentage) of patients in whom the desired effect occurred.

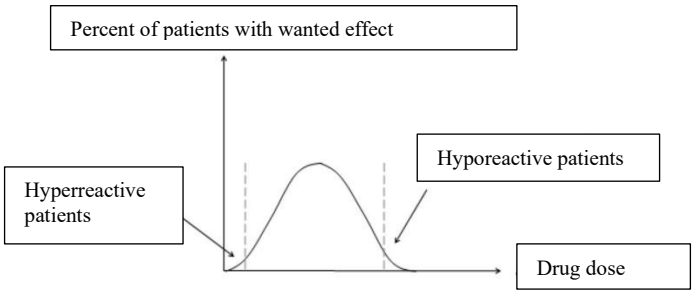
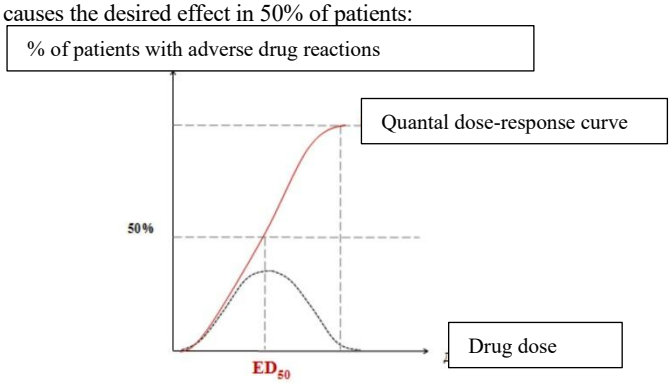


Figure 4. Gaussian Normal Variation Curve

Summing the responses for each dose forms a quantal dose-response curve. The ED50 in this case is the dose of drug that causes the desired effect in 50% of patients:



The median toxic dose and median lethal dose (TD50 and LD50) are determined in a similar way.

Figure 5. Quantal relationship between dose and drug effect.

DRUG-DRUG INTERACTIONS

Two drugs that are administered simultaneously can affect each other in such a way that their total effect is reduced or increased. This effect of one drug on the other can occur during their absorption, distribution, metabolism or excretion, when we talk about **pharmacokinetic interactions**, or at the very site of their action on the target tissue or organ (then we talk about **pharmacodynamic interactions**). If two drugs act together in such a way that their total effect is not reduced or increased, then such drugs are called synergists. **Synergism can be additive** (when the total effect of both drugs is equal to the simple sum of the effects of both drugs separately) or **potentiating** (when the total effect of both drugs is greater than the simple sum of the effects of both drugs separately). Nonsteroidal anti-inflammatory drugs behave additively, while potentiating synergism is shown, for example, by the combination of two chemotherapeutics, sulfamethoxazole and trimethoprim.

On the other hand, if two drugs act together in such a way that their total effect is less than the sum of their individual effects, we say that there is **antagonism** (note: this is antagonism between two drugs, not the antagonistic action of a drug on a receptor, which was discussed in the previous chapter). Antagonism can be chemical in nature, when two drugs chemically bind to each other and thus inactivate each other. An example of this is penicillin and gentamicin, which should never be administered in the same syringe. Drugs can antagonize each other's effects at all stages of their movement in the body: during absorption, distribution, metabolism and excretion, reducing the available amount of the drug near the receptor. An example of an interaction of two drugs during absorption is the simultaneous oral administration of doxycycline (a tetracycline antibiotic) and ferrous sulfate; iron binds to doxycycline, forming a complex that cannot be absorbed from the intestinal lumen into the bloodstream. During distribution, a potential site where drugs can interact with each other is plasma proteins, primarily albumin. Since a number of drugs are highly

bound to albumin, if administered simultaneously, they can interfere with each other's binding, increasing the concentration of the free fraction of the drug in plasma. However, an increase in the free fraction of a drug in plasma is accompanied by an acceleration of its metabolism, since it enters hepatocytes to a greater extent, so the end result of the interaction on albumin will not be an increase in the effect of the drug, i.e., these interactions are of no clinical significance. An example of a drug interaction during metabolism is the increase in the blood concentration of the antiepileptic drug carbamazepine when administered simultaneously with clarithromycin or erythromycin, antibiotics that inhibit cytochrome CYP 3A4 and thus interfere with the metabolism of carbamazepine. During drug excretion, a known example of an interaction with clinical significance is the increase in the blood concentration of the cardiotonic drug digoxin, which occurs due to the blockade of the tubular secretion of this drug by the antiarrhythmic amiodarone.

Drugs can act on the same organ in opposite directions. For example, adrenergic drugs dilate the bronchial tree while cholinergic drugs cause bronchoconstriction. Such drugs are **physiological antagonists**. If drugs bind to the same receptor and to the same site on the receptor, so that one of them has intrinsic activity and the other does not, but can only interfere with the binding of the first to the receptor, then we say that it is a **pharmacological antagonism**. The first drug, which has intrinsic activity, is called an agonist, and the second, which does not, is called an antagonist.

If the antagonist binds to the receptor non-covalently, then by increasing the concentration of the agonist we can displace the antagonist from the receptor and achieve the same effect with the agonist again. Such antagonism is called **competitive or reversible antagonism**. Examples of such antagonism include homatropine, which blocks muscarinic receptors, and pilocarpine, which activates them..

On the other hand, if the antagonist is bound to the receptor by covalent bonds, no matter how much we increase the concentration of the agonist, we cannot achieve the same effect as before the antagonist was applied. The reason for this is the fact that the receptors to which the antagonist has bound are irreversibly changed and rendered inoperative. We call such antagonism **non-competitive or irreversible antagonism**. The best-known examples of drugs that irreversibly block receptors are phenoxybenzamine (alpha receptor blocker) and proton pump blockers (omeprazole, pantoprazole and others).

There are drugs that have intrinsic activity after binding to a receptor (meaning they cause an effect), but it is significantly less than the intrinsic activity of other drugs that bind to the same receptor. We call such drugs **partial agonists**. If we use them together with drugs that have full intrinsic activity (**full agonists**), then partial agonists will reduce the effect of full agonists because they will occupy a number of receptors and will cause a smaller effect than full agonists. That is why partial agonists are often called **partial antagonists**. An example of a partial agonist is nalorphine. If it is used alone, it has a weak analgesic effect, but if it is used together with morphine (a full agonist), it will reduce the effect of morphine and behave as a partial antagonist.

THERAPEUTIC WINDOW AND THERAPEUTIC INDEX

Drug selectivity is the property of a drug to act only on one site in the body, without affecting the function of other tissues and organs. Unfortunately, no drug is absolutely selective, but more or less affects other sites in the body. Often these other effects are unfavorable for the body, so we call them **adverse effects**. If they involve significant damage to the body's tissues and if they occur when the drug is administered in doses higher than recommended, we call them **toxic effects**. The range between the minimum dose of the drug that causes a favorable effect in the body and the minimum dose of the drug that causes a toxic effect is called the **therapeutic window** of the drug. The greater the therapeutic window, the more suitable the drug is for use.

Another measure of the selectivity of the drug's effect is the **therapeutic index**. It is the ratio of the dose of the drug that causes a toxic effect in 50% of patients (TD50) to the dose of the drug that causes the desired effect in 50% of patients (ED50). The mathematical expression for the therapeutic index (TI) is:

$$TI = \frac{TD_{50}}{ED_{50}}$$

(ED_{50}) and (TD_{50}) can be easily determined using dose-response curves, if we read on the abscissa the drug concentrations that lead to the desired, and toxic effects in 50% of patients, as seen in the figure.

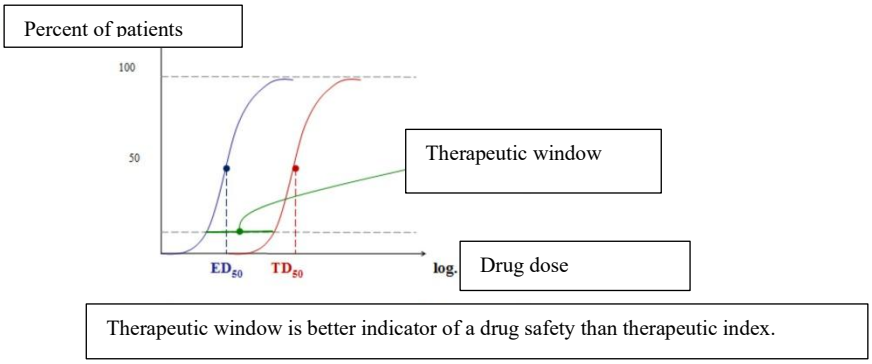


Figure 6. Therapeutic window and therapeutic index.

If a drug has a larger therapeutic index (similar to the therapeutic index), its use is easier and safer. Since a drug can have multiple side effects, it will have multiple therapeutic indices: as many as there are side effects. Sometimes the therapeutic index for some of the milder side effects is called the **protective index** (for example, the ratio of the ED50 of phenobarbitone for sedative effect to the ED50 of phenobarbitone for anticonvulsant effect (prevention of convulsions).

FAMILIES OF RECEPTORS

Receptors for most drugs and endogenous substances can be classified into several groups based on their similar mechanisms of action. Since each of these groups is thought to have evolved from a common ancestor—a "primitive receptor"—we call them receptor families. We currently know of four major families, or superfamilies: ion channel receptors, membrane enzyme receptors, G-protein-coupled receptors, and intracellular receptors.

Receptors that are ion channels are located in the cell membrane and are closed in the resting state. When an agonist (drug or endogenous substance) binds to such a receptor, it undergoes conformational changes, creating an opening (channel) through which ions can pass. Since ions are present in different concentrations on both sides of the membrane, they now pass through the channel from a place of higher to a place of lower concentration. Depending on the type of ion, the consequence of this movement will be depolarization or hyperpolarization of the cell membrane. The best known ion channel receptors are nicotinic receptors (sodium ion channels) and receptors for excitatory (aspartate, glutamate) and inhibitory (gamma-aminobutyric acid-GABA) amino acids. The time elapsed from the moment of binding of the drug to such receptors until the onset of the effect is measured in milliseconds.

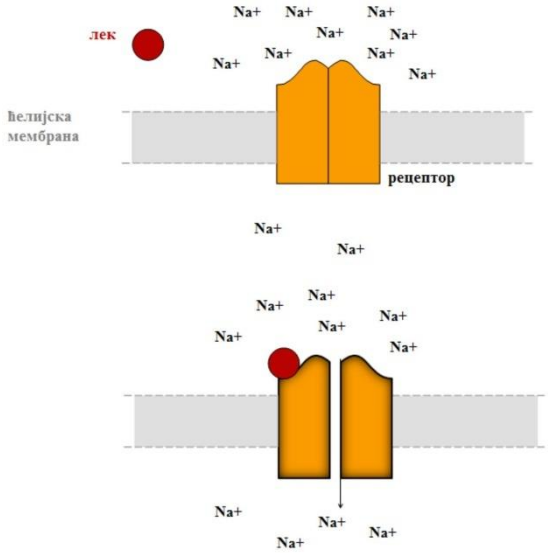


Figure 7. Receptors ion channels.

Another superfamily of receptors is also found in cell membranes, functioning as **membrane enzymes**. The receptor spans the lipid bilayer of the membrane, so it has two functional parts: one on the outside of the membrane to which drugs (or endogenous substances) bind, and the other on the inside, which functions as an enzyme. At rest, the enzymatic part of the receptor is inactive; however, after a drug binds to the outer part of the receptor, it is activated and catalyzes a certain biochemical reaction. The receptor for the hormone insulin belongs to this group. Its enzymatic part behaves like a tyrosine kinase, i.e., it phosphorylates the amino acid tyrosine in intracellular enzymes, leading to their activation. The time that elapses from the binding of the drug to the receptor to the onset of the effect is measured in minutes.

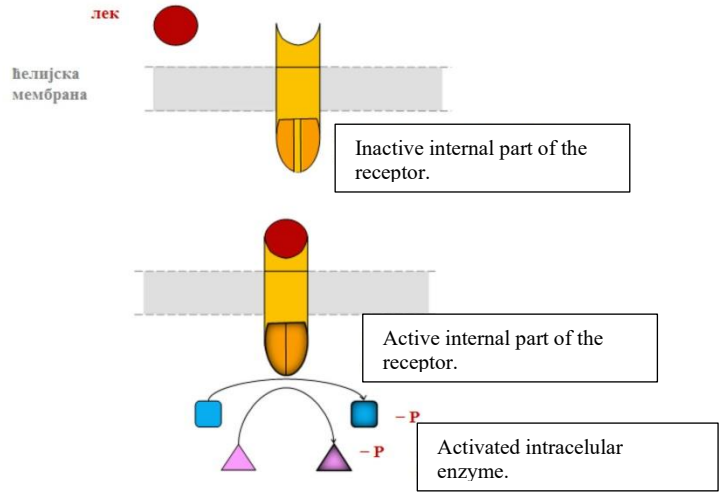


Figure 8. Receptors transmembrane enzymes.

One subtype of transmembrane enzyme receptors are **cytokine receptors** (growth hormone, erythropoietin, interferons, and others). In these, the part of the receptor on the inner side of the membrane is not an enzyme, but is in close contact with an enzyme; most often, this enzyme is a tyrosine kinase, from the family of so-called "**Janus kinases**", which becomes active when the receptor affects it. This tyrosine kinase phosphorylates a group of proteins called "signal transmitters and activators of transcription" (PSAT). After phosphorylation, PSAT goes to the nucleus and there regulates the transcription of certain genes.

Receptors linked to G-proteins are very numerous. These include: adrenergic alpha and beta receptors, muscarinic receptors, dopamine receptors, and many others. They are structurally characterized by the fact that their peptide chain passes from end to end of the cell membrane seven times.

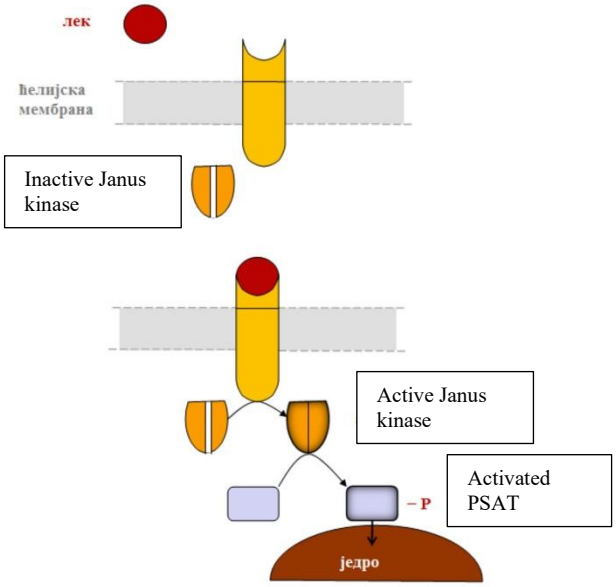


Figure 9. Receptors for cytokines.

Drugs or endogenous substances (also called endogenous ligands) bind to the part of the receptor on the outside of the membrane and cause conformational changes so that the intracellular part is activated. The thus activated intracellular part of the receptor interacts with the G-protein. G-proteins are located on the inside of the membrane and consist of three subunits, alpha, beta and gama. They are called G-proteins because after interacting with the intracellular part of the receptor, they bind guanosine triphosphate (GTP) to the alpha subunit, while the beta and gama subunits dissociate. The thus activated alpha subunit can have different functions inside the cell, depending on the type of G-protein. In some G-proteins, it stimulates, and in some it inhibits, the enzyme adenylate cyclase, which otherwise produces cyclic adenosine monophosphate (cAMP), an important intracellular second messenger. In the third group of G-proteins, the alpha subunit activates the enzyme phospholipase C, which converts the membrane phospholipid phosphatidyl-inositol into two secondary intracellular messengers: diacyl-glycerol and inositol-triphosphate. All secondary messengers further activate or inhibit various intracellular functional proteins, which ultimately leads to a cell reaction (in the case of a muscle cell, it contracts or relaxes, and in the case of an exocrine or endocrine gland cell, it secretes its product). In order to exert its effect, the alpha subunit requires energy. It obtains it by breaking down GTP into guanosine diphosphate (GDP) and phosphoric acid. After exerting its effect, the alpha subunit is inactivated by the action of GDP, binds again to the beta and gama subunits, and the entire G-protein enters a resting state that lasts until the drug binds to the receptor again.

The time from drug binding to receptor to onset of effect is measured in seconds.

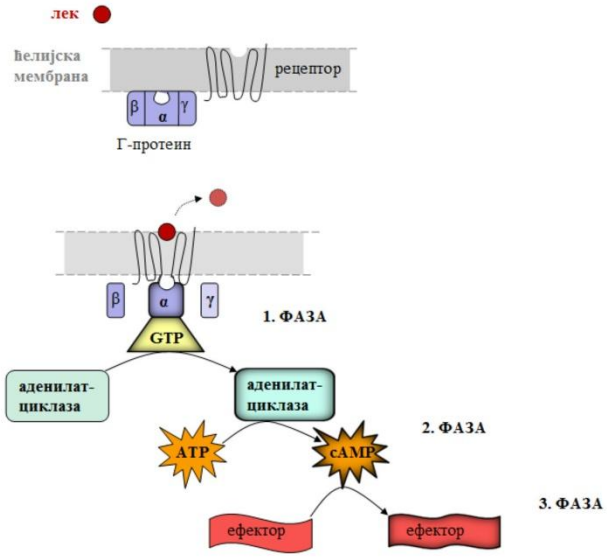


Figure 10. G-protein bound receptors.

Intracellular receptors (some of which are in the cytoplasm and some in the nucleus) can only bind substances that are liposoluble, i.e., that can freely diffuse through the lipid layer of the cell membrane. These are primarily steroid hormones (glucocorticoids, estrogens, androgens, progesterone), thyroid hormones, and liposoluble vitamins A and D. Binding of these substances to the receptor leads to the formation of a drug-receptor complex that regulates gene expression: it increases the transcription of some genes and decreases the transcription of others. The end result is increased synthesis of enzymes and other functional proteins of the cell. Since protein synthesis takes time, these drugs exert their clinical effects only after a latent period (the first effects are seen after one hour, and the full effect only after 24 hours)..

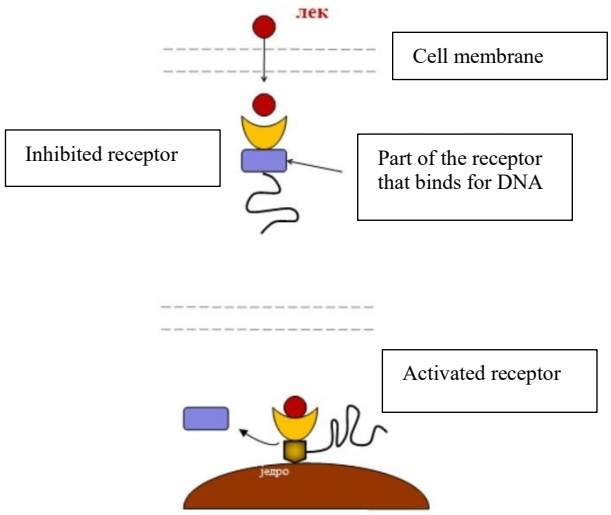


Figure 11. Intracellular receptor.

SECOND MESSINGERS

As mentioned in the previous chapter, receptor activation by a drug leads to the production of signaling molecules inside the cell, which initiate a series of changes in the cell and ultimately lead to an effect (e.g., contraction, secretion, etc.). Such signaling molecules are called second messengers. The most important second messengers are cyclic adenosine monophosphate (cAMP), calcium and phosphoinositides, and cyclic guanosine monophosphate (cGMP). Second messengers allow the amplification of the signal generated by the binding of the agonist to the receptor.

Cyclic adenosine monophosphate (cAMP) is formed from adenosine triphosphate (ATP) by adenylate cyclase. cAMP binds to protein kinases, which phosphorylate the corresponding enzymes in the cell, thus activating them. Depending on the type of enzymes present in the cell, a certain type of effect will occur. For example, in the heart, an increase in cAMP leads to an increase in the force of myocardial contraction. The action of cAMP is terminated by its degradation, under the influence of the enzyme phosphodiesterase.

Some of the G-protein-coupled receptors and transmembrane enzyme receptors, after activation by an agonist, can activate the membrane enzyme phospholipase C. This enzyme breaks down a phospholipid from the cell membrane, phosphatidylinositol-4,5-biphosphate, into two second messengers: **diacylglycerol and inositol-1,4,5-triphosphate**. The diacylglycerol remains in the membrane, and there it activates another membrane enzyme, protein kinase C. The inositol-1,4,5-triphosphate moves into the cytoplasm, and leads to the release of calcium ions from intracellular depots (endoplasmic or sarcoplasmic reticulum). The released calcium binds to the protein calmodulin in the cytoplasm, and the resulting compound further regulates the activity of protein kinases in the cell.

The activity of inositol-1,4,5-triphosphate is terminated by dephosphorylation, and diacylglycerol is either incorporated back into phospholipids or completely degraded.

Cyclic guanosine monophosphate functions as a second messenger in only a few cell types, including intestinal mucosal cells and vascular smooth muscle cells. In vascular smooth muscle cells, cGMP regulates the activity of enzymes from the kinase group, which ultimately leads to dephosphorylation of myosin light chains and relaxation of the cell. cGMP is produced by either cytoplasmic guanylyl cyclase or membrane guanylyl cyclase. The cytoplasmic enzyme is activated by nitric oxide (NO), previously produced in endothelial cells, under the influence of acetylcholine, histamine, or some other mediators. Membrane guanylyl cyclase is actually the inner part of the receptor of the transmembrane enzyme, which binds the hormone atrial natriuretic peptide (ANP) from the outside of the membrane.

Note the fact that almost all second messengers ultimately use the mechanism of **reversible phosphorylation** to further transmit information within the cell. In the last two decades, intensive work has been carried out on the development of drugs that can inhibit protein kinases, and thus prevent phosphorylation. One such drug (imatinib) has been used for many years with remarkable success in the treatment of chronic myeloid leukemia, because it blocks the cytoplasmic tyrosine kinase in malignant cells, which is otherwise activated by growth factors.

BIOLOGICAL STANDARDIZATION

Some drugs cannot be produced in pure form, but only as preparations in which the exact amount of the active substance is not known. In order to dose such drugs (usually vitamins or hormones: vitamin D, insulin, etc.), the produced preparations are administered to experimental animals (or some other model, e.g., cell culture) and their activity is compared with the activity of standard preparations. A certain amount of the standard is designated as one international unit (IU). The preparation being tested contains as many international units of the active substance as it is times more active than one international unit of the standard.

Over time, due to advances in pharmaceutical technology, some preparations that were previously measured using international units were synthesized or isolated in pure form. Then, the dose was simply measured in weight units (for example, 1 international unit of vitamin D3 contains 0.025 mcg of pure substance).

PHARMACOKINETICS

Absorption and distribution of drugs

Absorption

The movement of drugs in the body begins with the process of absorption. Drug absorption is the process of moving a drug from the site of administration to the bloodstream. On this path, the only real obstacle is the lipid membranes through which the drug can pass in one of two most important ways: by diffusion, provided that it is sufficiently lipophilic, and by specific transport (active or facilitated), with the help of a specific carrier and with the expenditure of energy. The second way is much less common, so most drugs can be absorbed only if they become sufficiently lipophilic. Since most drugs are chemically either weak acids or weak bases, they will be more lipophilic if they are less ionized, i.e., less dissociated. The degree of their ionization is most affected by the pH of the environment in which the drugs are found. If the environment is more acidic (low pH), then drugs that are weak acids will be mostly unionized, and thus lipophilic, which means that they will easily pass through lipid membranes. In contrast, drugs that are weak bases will be highly ionized and will pass very poorly through lipid membranes. The opposite happens if the environment is more basic (high pH): then drugs that are weak acids will be ionized, and drugs that are weak bases will be unionized.

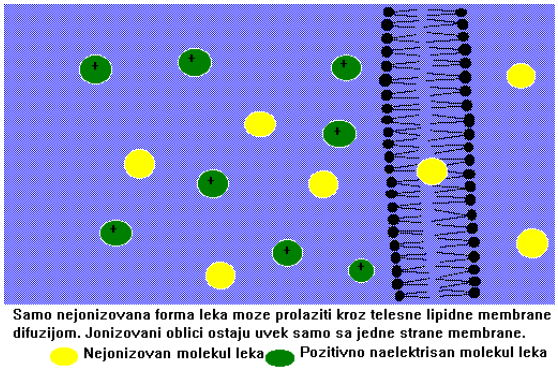


Figure 12. Passage of drugs through lipid membranes.

Therefore, the pH of the environment is one of the most important factors that affects the absorption of drugs by changing their ionization, or lipophilicity. The influence of the pH of the environment on the ionization of drugs is not linear, but sigmoidal: small changes in pH lead to large changes in the ionization of drugs, and thus their absorption.

A number of drugs pass through the enterocyte membrane by specific transport, using protein molecules – transporters in the membrane. The superfamily of organic anion-transporting polypeptides (the English abbreviation is **organic anion-transporting polypeptide** [OATP]) is located in the membrane of enterocytes, but also in the membranes of other cells in the body, especially hepatocytes. The superfamily has a total of 11 members, which are grouped into 6 families. The most important transporters are OATP2B1 and OATP1B, which are found on both enterocytes and hepatocytes. These transporters are also important in drug-drug interactions and drug-food interactions. For example, some components of orange and apple juice inhibit the OATP2B1 transporter in enterocytes and interfere with the absorption of drugs that use it, e.g., the antihistamine fexofenadine.

In addition to diffusion or specific transport, small amounts of drugs can pass through the lipid membrane by **endocytosis**. This is mainly the case for drugs whose molecules are proteinaceous in nature. Only drugs with a molecular weight below 100 Daltons can use another way to pass through lipid membranes: filtration, i.e., free passage through water pores in the membranes. There are few such drugs (e.g., ethanol, urea), so this way of passing through membranes is not of great importance.

We can bypass drug absorption if we administer the drug as an **intravenous injection**. Then, through a needle inserted into a vein, we directly inject the drug into the blood. This method of administering drugs allows for the drug to reach the blood quickly and completely, and to start working quickly, which is very important in emergency situations. However, this method of administration is also very risky: the drug must be administered slowly enough (an intravenous injection should always be given over more than two to three minutes), otherwise the concentration of the drug in the blood can instantly increase so much that it reaches a toxic level. With drugs that affect the heart rhythm, severe rhythm disturbances and almost immediate death can occur. Intravenous administration of drugs carries a high risk of infection with Staphylococcus, hepatitis virus, or the causative agent of AIDS. It should always be kept in mind that emulsions and suspensions of drugs should not be administered intravenously due to the occurrence of lipid embolism; in addition, any injection of air or gas intravenously leads to air embolism. One way to reduce the risks of intravenous drug injection is to administer drugs in the form of intravenous infusion: the drug is dissolved in more

than 100 ml of simple saline and administered drop by drop through a needle inserted into the patient's vein. This ensures the gradual entry of the drug into the blood and avoids the possibility of high, toxic drug concentrations. Intravenous infusion can be continuous, when it is administered without interruption, or intermittent, when after the appropriate dose has been administered, it is interrupted until the next dose is administered. The rate of intravenous infusion depends on the diameter of the intravenous set, which determines how many drops are in one milliliter of solution, and on the number of drops per minute to which we adjust the drip chamber using a clamp with a dial.

All routes of drug administration except the oral and rectal routes are called **parenteral drug administration**. Intravenous administration of drugs is one form of parenteral administration. Other methods of parenteral administration of drugs are subcutaneous injection, intramuscular injection, intrathecal and epidural injection, transdermal administration, and administration via the respiratory tract.

Subcutaneous and intramuscular drug injections involve the administration of a drug through a needle into the subcutaneous or muscular tissue. The drug must be absorbed from the site of administration in order to reach the blood. Since the capillaries in the subcutaneous and muscular tissue have large pores (they allow protein molecules up to 60,000 D molecular weight to pass through), all drugs are absorbed by simple diffusion, regardless of whether they are ionized or not. Absorption primarily depends on the solubility of the drug and the speed of blood flow in the tissue. Due to the better blood supply to the muscular tissue, drugs are absorbed much faster after intramuscular than after subcutaneous administration. These routes can also be used to administer highly ionized drugs that are not otherwise absorbed at all from the gastrointestinal tract. Drugs that are highly irritating to tissue are not administered as subcutaneous injections, as they can lead to skin necrosis, most likely due to thrombosis of the blood vessels that supply the dermis from the subcutaneous tissue.

Drugs for subcutaneous or intramuscular injection are sometimes intentionally prepared so that the absorption of the drug is greatly slowed down, in order to maintain sufficient drug concentrations in the blood for a long time (sometimes weeks). This is usually done either by forming esters of the drug with long-chain fatty acids that are slowly degraded, or by placing the drug in a medium that is difficult to absorb. Such preparations are called **depot injections**. The antipsychotic risperidone is also produced as a depot preparation; in this case, the drug is enclosed in biodegradable microspheres made of poly (d,l-lactide-co-glycolide). After injection into the muscle, risperidone begins to be gradually released into the blood as the microspheres break down, so that the drug is present in the blood for up to 6 weeks. Injections every 2 weeks ensure stable concentrations of risperidone in the blood, and thus the therapeutic effect.

Intrathecal administration of a drug involves injecting the drug into the subarachnoid space, i.e., into the cerebrospinal fluid. ***Epidural administration*** of a drug involves injecting the drug into the epidural space, i.e., outside the dura mater. Both types of injection are administered in the lumbar region, between the L3 and L4 vertebrae. Intrathecal administration was once widely used to treat bacterial meningitis and encephalitis with antibiotics that have poor penetration into the central nervous system (penicillins, aminoglycosides). However, it has been shown that such administration of antibiotics is associated with a high incidence of arachnoiditis and epileptic seizures, so this practice has been abandoned. Today, these forms of drug administration (epidural injection) are widely used to treat severe pain in malignant diseases, because morphine can be administered in very small doses, and its effect lasts much longer than after conventional administration.

We can only administer drugs that are highly liposoluble ***transdermally,*** because the epidermis can be viewed as a multiple lipid membrane. The drug is dissolved in a suitable medium and brought into contact with the skin with the help of an adhesive tape. The absorption of the drug is slow, so that high drug concentrations are maintained in the blood for a long time. It is even more important that this administration avoids the drug from immediately passing through the liver, thereby prolonging the life of those drugs that are metabolized very quickly in the blood. Today, the most commonly administered in this way are nitroglycerin, an organic nitrate with a beneficial effect on angina pectoris, and fentanyl, an opioid analgesic for the treatment of pain in cancer patients..

We can also administer drugs via the ***respiratory tract***. Beta-adrenergic agonists are most commonly used because of their local effect in the treatment of asthma attacks (they relax the bronchial muscles). Anesthetic gases and vapors are also administered via the respiratory tract, but because of their effect on the central nervous system. This route of administration is very fast and effective (the surface area of the alveolar membrane of the lungs is as much as $70m^2$, and its thickness is only 0.2 micrometers), but it is difficult to control, and is associated with the risk of overdose.

By far the most common method of administering drugs remains ***oral administration***. It is the simplest and easiest for the patient - they only need to swallow the drug. Oral administration is also the safest, because the absorption of the drug is significantly slower compared to other methods of administration, so the drug rarely reaches highly toxic concentrations in the blood. Drugs are practically not absorbed in the stomach, except for: (1) small amounts of drugs that are weak acids (e.g., acetylsalicylic acid, paracetamol, ascorbic acid, etc.) and (2) alcohol. However, the stomach can act as a "**waste basin**" for weak base drugs, even if they are administered parenterally. Weak base drugs are largely undissociated in the blood, so they easily

diffuse from the blood, through the stomach wall, into its lumen. Due to the high acidity of the gastric juice, drug molecules that have reached the stomach lumen dissociate, and thus become polar, i.e., they can no longer return through the stomach wall back into the blood (this is also popularly called "**ion trapping**"). In this way, a part of the weak base drug is withdrawn from the systemic circulation into the stomach lumen, thus weakening the overall effect of the drug on the target tissue.

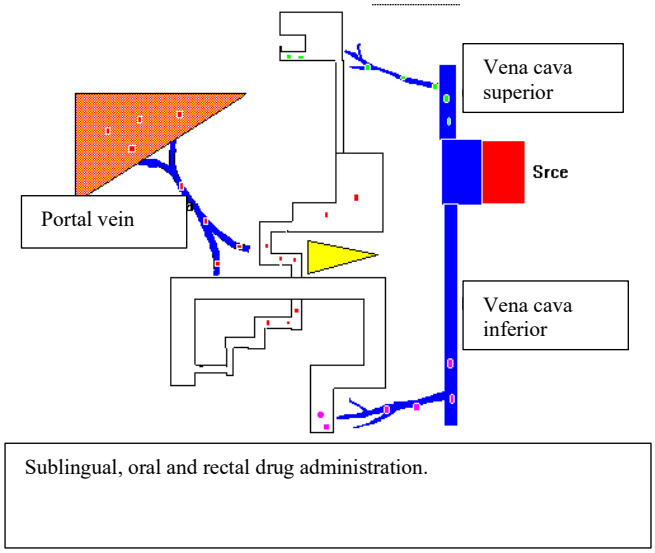


Figure 13. Absorption from gastrointestinal tract.

Most drug absorption occurs **in the small intestine**, which is characterized by a very large absorption surface and excellent blood supply (drugs are absorbed primarily in the first 1-2 meters of the jejunum). The intestinal epithelium acts as a lipid membrane through which drugs pass either by diffusion (if they are sufficiently lipophilic) or by active transport (if they have a specific transporter). Many factors affect the absorption of drugs from the digestive tract. First, the rate of gastric emptying determines the speed at which the drug will reach the site of absorption, i.e., the small intestine. A drug taken before a meal reaches the small intestine quickly, after 10 to 15 minutes. However, if it is taken after a meal, the entire amount of the drug will reach the small intestine only when the stomach is completely empty, which means after 3 to 5 hours. Second, the rate of peristalsis of the small intestine can have a significant effect on absorption. If the rate is too high (as in all forms of diarrhea), the drug will reach the large intestine before significant absorption has occurred. Third, the food that the patient consumes during the administration of the drug can significantly affect absorption. For example, if the patient consumes dairy products while taking tetracycline, a large part of the tetracycline will form insoluble complexes with calcium from the milk, which will be eliminated in the stool. In this way, the absorption of tetracycline will be significantly reduced.

Sometimes patients have difficulty tolerating a drug taken orally, and feel nauseated, which may lead them to stop taking the drug. This is especially common with drugs that irritate the gastric mucosa, e.g., iron preparations, tetracyclines, serotonin reuptake blockers. In such a situation, patients should be advised to try to take the drug with a meal, or, if the drug is given in only one daily dose, to take the drug just before going to bed.

Two other distinct processes affect drug absorption in the small intestine. Since drugs actually pass through epithelial cells during absorption, they are also affected by the detoxification mechanisms that these cells have.

The first detoxification mechanism **is drug metabolism in the endoplasmic reticulum of epithelial cells**, on cytochrome P450. So far, isoforms 3A4, 3A5, 2C9, and 2C19 of this cytochrome have been discovered in the epithelial cells of the small intestine, which can inactivate a large part of the drug that is absorbed, and thus prevent it from entering the blood. For example, due to these enzymes in epithelial cells, only 20% of the orally administered immunosuppressant cyclosporine reaches the blood unchanged. Another mechanism that hinders drug absorption in the small intestine are **pumps (transporters) on the luminal membrane of epithelial cells**, which expel the drug that has entered the cell back into the lumen. The most important of these pumps is glycoprotein P. Interestingly, there are a large number of drugs that are simultaneously substrates for cytochrome 3A4 and glycoprotein P, and thus their absorption in the small intestine is hindered on two grounds.

All drugs absorbed in the gastrointestinal tract reach the liver first through the portal circulation. If the drug is extensively metabolized in the liver, only a small percentage of the administered amount will reach the systemic circulation. Such drugs are said to undergo **first-pass metabolism**. The best-known example of such drugs are organic nitrates, whose metabolism is so rapid that oral administration is only possible if the drug dose is tenfold increased.

Only if the drug is administered intravenously does the entire dose reach the systemic circulation. With all other routes of administration, only a portion of the drug dose reaches the systemic circulation (this is especially pronounced with oral administration, where a large portion of the dose is not absorbed or is degraded during the first pass through the liver). The **bioavailability of a drug** is the fraction (or percentage) of the drug that reaches the systemic circulation. For example, the bioavailability of the opioid analgesic morphine is about 25%, which means that of a 40 mg oral dose of this drug, only 25%, i.e., 10 mg, will reach the systemic circulation from where it can pass into the central nervous system and exert its effect. We determine the bioavailability of a drug by administering the drug both orally and intravenously; then we measure the drug concentrations in the serum every hour after drug administration, and form serum drug concentration/time curves for both routes of administration (in a coordinate system where the x-axis is the time elapsed since drug administration, and the y-axis is the drug concentration in the serum). When we calculate the area under the serum drug concentration/time curve after oral administration and the area under the serum drug concentration/time curve after intravenous administration, and divide one by the other (AUCoral/AUCintravenous), we obtain the so-called **absolute bioavailability** of the drug. **Relative bioavailability** is calculated when comparing two different medicinal products with the same active substance, after the same route of administration.

To avoid the effect of the first pass through the liver, many medicines are administered sublingually, buccally or rectally (Figure 13). Sublingually, we administer medicines by placing a specially prepared tablet called a lingual tablet under the tongue and waiting for it to dissolve in the mouth. Buccal administration is carried out according to the same principle, only the buccal tablet is placed in the sulcus between the gum and the mucous membrane of the cheek. In both cases, the resorption of the drug is very rapid and the liver is bypassed, because the drugs reach the systemic circulation directly through the superior vena cava system. However, the condition for this type of administration is the high liposolubility of the drug. Organic nitrates are most often used in this way to treat angina pectoris attacks.

Rectal administration can also bypass the liver. A drug administered in the form of a suppository will be absorbed in the lower two-thirds of the rectum. Since the inferior and middle hemorrhoidal veins that drain blood from the lower two-thirds of the rectum flow directly into the inferior vena cava system, the drug will not have to immediately pass through the hepatic circulation. Also, we administer rectally drugs that irritate the gastric mucosa in patients who already have a stomach disease (gastritis, ulcer); if patients cannot take drugs orally due to prolonged vomiting, rectal administration also remains an alternative. An example of rectal administration of drugs is the use of suppositories with paracetamol in children who have a high fever accompanied by vomiting.

New drug delivery systems

Much has been done recently to develop new drug delivery systems that allow greater control over drug concentrations in the blood after absorption in terms of height and duration. Some of these systems are listed in the text that follows. **The bead system** is used for oral drug administration. The capsule contains numerous beads of inert material (usually polystyrene, i.e. the material from which Styrofoam is made) that are coated with a layer of drug. When the beads are released from the capsule, the drug is released slowly from them, so absorption is prolonged and the drug remains in the patient's blood for a longer time, with its concentrations being lower than in ordinary oral preparations. This results in the drug acting longer and the side effects (which occur at higher concentrations) being less pronounced**. Immunoliposomes** are currently the most advanced method for the targeted delivery of highly toxic cytostatics to tumor cells. Ordinary liposomes are tiny spheres made of two or more layers of phospholipids, which contain a drug, e.g., the cytostatic doxorubicin. In immunoliposomes, the phospholipid layer contains the variable part of a monoclonal antibody against an antigen on a tumor or other cell. When immunoliposomes are injected intravenously into a patient, they accumulate more in tumor tissue, whose capillaries are more permeable than in normal tissues, and then bind to antigens on tumor cells via the variable part of the monoclonal antibody. Then, tissue enzymes break down the liposomes, and the drug (e.g., the cytostatic) is released into the tumor tissue itself and penetrates the tumor cells. The administration of drugs contained in **nanoparticles (balls) of branched polyesters that are non-toxic and rapidly degradable, or in liposomes, by inhalation** allows the drug to remain in the lung tissue for a longer time, and thus requires less frequent dosing. In this way (by inhalation of nanoparticles), the prostaglandin analogue iloprost is administered in the treatment of pulmonary hypertension. **Selective release of the drug from the capsule in the large intestine** is very important when a direct effect on that organ is desired (e.g. the use of sulfasalazine in ulcerative colitis) or when the drugs themselves are sensitive to the effects of gastric acid or pancreatic enzymes (e.g., peptides). This is achieved by making capsules of polysaccharides (primarily

galactomannan) that do not disintegrate in the stomach and small intestine, but only when they reach the large intestine, under the influence of bacteria.

Distribution

After reaching the blood, drugs move further in the body to all tissues. We call this process **drug distribution**. How far the drug will reach in the body, i.e. which tissues it will penetrate, depends mostly on its physicochemical characteristics, i.e., on its molecular structure. If we know the structural formula of the drug, we can very easily predict its movement in the body. The most important molecular characteristic of the drug that determines its movement in the body is the ionization of the molecule at physiological pH values in body fluids. We can view each water-soluble drug as a weak acid or base, so its degree of ionization will depend on the pH of the environment in which it is currently located. On the other hand, liposoluble drugs can be considered practically undissociated at any pH of the environment.

Water-soluble drugs are mostly ionized at pH = 7.36 - 7.40, which is the normal concentration of hydrogen ions in the blood and extracellular fluid. If such drugs have molecules larger than 100 Daltons (which is the case with most drugs), they can pass through body membranes (which are actually continuous lipid layers) in only two ways: by gradual diffusion of non-ionized molecules (which are then liposolubles) through the membrane or with the help of a specific protein transport system in the membrane. Since a specific transport system exists only rarely, most water-soluble drugs pass through membranes very slowly and insufficiently. We are particularly interested in the passage of drugs through the blood-brain barrier, which can also be considered a continuous lipid layer (the endothelial cells in the capillaries of the brain are tightly connected to each other so that there is no free passage between them). Only liposoluble drugs with a molecular weight of less than 400 daltons and those water-soluble drugs, i.e., liposoluble drugs with large molecules, for which there are specific transport systems, penetrate the central nervous system (CNS) to a significant extent. It is clear that these will be those drugs that, in terms of their chemical structure, resemble endogenous water-soluble substances (e.g. amino acids) for which transport systems have been created during evolution because they are necessary for the normal functioning of the CNS. One such drug is alpha-methyldopa, an antihypertensive with central action. Interestingly, the testicles contain a hemato-testicular membrane that has similar characteristics to the hematoencephalic membrane.

Within the blood-brain barrier, there are several transporters that drugs can use to enter the brain tissue from the blood: the **glucose transporter GLUT1, the monocarboxylic acid transporter (MCT1), the neutral amino acid transporter (LAT1), the basic amino acid transporter (CAT1), and the purine nucleoside transporter (CNT2)**. On the other hand, in the blood-brain barrier, in endothelial cells, there is the same efflux pump (glycoprotein P) that pumps drugs that penetrate the endothelial cells back into the blood. This pump is also called the ATP-binding cassette (ABC), because it consumes energy, with the special designation B1 (ABCB1). In addition to glycoprotein P, there are other ATP-binding cassettes that can pump drugs back into the blood.

Inflammation of the brain or its membranes (encephalitis or meningitis) significantly increases the permeability of the blood-brain barrier, so that antibiotics can penetrate more easily and exert their effect. For example, penicillin penetrates the blood-brain barrier in a healthy person by only 1-2%, but when meningitis or encephalitis occurs, the penetration of this drug increases to 10%.

Much work is being done to develop water-soluble drug formulations where they are bound to nanoparticles, in order to increase their penetration through the blood-brain barrier. Nanoparticles are made of degradable polymers, and drug molecules are attached to them in various ways. When a nanoparticle reaches the brain capillaries, it binds to receptors on the surface of endothelial cells, which then endocytosis the nanoparticle together with the drug. So far, nanoparticles with doxorubicin have been used successfully to treat malignant brain tumors.

An important segment of intracranial drug movement is their presence in the cerebrospinal fluid. Cerebrospinal fluid is formed in the choroid plexus of the cerebral ventricles, exits through the openings in the roof of the fourth cerebral ventricle, moves along the surface of the brain and enters the bloodstream via the arachnoid nodules in the superior sagittal sinus. There is a total of about 130 milliliters of cerebrospinal fluid, and it is completely replaced in 4-5 hours. Drugs relatively easily enter the cerebrospinal fluid, but from it they very quickly leave back into the bloodstream, because the absorption of drugs in the arachnoid nodules is many times faster than their diffusion into the brain tissue. Extremely little drug from the cerebrospinal fluid reaches the brain tissue.

In other tissues, drugs generally freely penetrate from the blood vessels into the intercellular spaces. Between the endothelial cells of the capillaries there are large openings through which most drugs can easily pass, except for those with a high molecular weight (proteins). The placenta also behaves similarly, so we can practically not talk about a placental barrier during pregnancy.

We can count on the fact that almost every drug that we give to the mother will also reach the fetus's bloodstream. When it comes to the mammary gland, we cannot count on a more serious barrier to the passage of drugs. Drugs can reach the milk by diffusion or active transport. Since milk is slightly acidic (pH 6.5), drugs that are weak bases tend to accumulate in the milk. Drugs that bind to milk components (e.g., tetracyclines for calcium, liposoluble drugs for milk fats) also have a similar tendency to accumulate.

If we talk about liposoluble drugs, there are practically no barriers for them in the body. Not only do they easily penetrate all tissues, they also tend to accumulate in tissues, especially adipose tissue. In addition, since water dipoles tend to displace them, they always bind to a high percentage of plasma proteins (most often albumin) that are rich in hydrophobic domains. A drug bound to a plasma protein does not exert its pharmacological effect because it is not in the vicinity of its receptor; therefore, the part of the drug bound to albumin can be viewed as a kind of **depot**. Of course, it is in equilibrium with the free drug in the plasma: as soon as the concentration of the free drug decreases, the bound drug is released from its protein binding, and vice versa. Drugs that are weak acids or weak bases also bind to plasma proteins. Weak acid drugs bind primarily to albumin, while weak base drugs bind to alpha1-acid glycoprotein and lipoproteins. The same applies to them as to liposoluble drugs: the part of the drug that is bound to proteins is in dynamic equilibrium with the part of the drug that is free in the plasma.

The binding of drugs to plasma proteins is nonspecific, so that a large number of drugs can bind to the same site. This means that, when administered simultaneously, two or more drugs can displace each other from the binding sites on plasma proteins, thereby changing the concentration of the free part of the drug in the plasma (which means that the intensity of the drug's effect also changes). For example, if a patient who has been taking the anticoagulant warfarin for months is given furosemide, a loop diuretic, the newly administered drug will displace warfarin from plasma proteins, and increase the concentration of free warfarin in the plasma. Due to the higher concentration of free warfarin in the plasma, its anticoagulant effect could be enhanced, which could theoretically cause bleeding in many organs in the patient (e.g., bleeding in the brain). However, such consequences of the above interaction occur very rarely or not at all, because any increase in the concentration of free warfarin in the plasma also leads to an acceleration of its metabolism, so the concentration almost never reaches the toxic range.

The binding of drugs to plasma proteins can also be affected by some pathological conditions. For example, in patients with uremia, the binding of weakly acidic drugs to plasma proteins is reduced (penicillin, salicylates, barbiturates, sulfonamides).

Some drugs have a high affinity for hydroxyapatite of bone tissue, so they accumulate in the bones in significant quantities. It is also a kind of drug depot in the body, but the balance between it and the free drug in plasma and interstitial fluid is established extremely slowly. Therefore, drugs that bind to bones once remain there for many years, even decades. This is the case with bisphosphonates, tetracyclines, lead, strontium and cisplatin.

It has long been known that the kidneys accumulate metals, which can gradually lead to the loss of function of this vital organ. The reason for the accumulation of metals in the kidneys is the protein **metallothionein**, which has a high affinity for lead, mercury and cadmium.

The eye can also be a place for the accumulation of drugs, which have an affinity for the pigment of the retina, melanin. Chlorpromazine, chloroquine, ethambutol and indomethacin are such drugs, which due to their accumulation in the retina can lead to visual impairment.

Redistribution phenomenon

Some drugs migrate from one tissue to another after administration: they redistribute. This usually happens after intravenous administration of liposoluble drugs. Since the blood flow through the brain is extremely high (1200 ml per minute), these drugs, after injection (when the concentration in the blood is high), reach the brain capillaries in large quantities, diffuse through the blood-brain barrier and achieve high concentrations in the brain tissue. That is why their effect on the CNS occurs very quickly after administration (e.g., the barbiturate thiopentone sodium causes the patient to lose consciousness while it is still being injected into the vein). However, when the injection is complete and a few more minutes have passed, liposoluble drugs diffuse increasingly into other tissues (muscle and fat), so that their concentration in the blood drops. This has the consequence that the drug now diffuses back from the brain tissue into the blood; the concentration of the drug in the brain tissue drops sharply and the effect of the drug on the CNS ceases (the patient regains consciousness 5-6 minutes after the administration of thiopentone sodium). The drug actually moves from the brain tissue into muscle and fat. The clinical consequence of the redistribution of thiopentone sodium is a short duration of anesthesia after its intravenous administration.

Volume of distribution

The volume of distribution (Vd) is a virtual quantity calculated as the quotient between the dose of the drug administered (D) and its concentration in the blood (Cp):

$$V_d = \frac{D}{C_p}$$

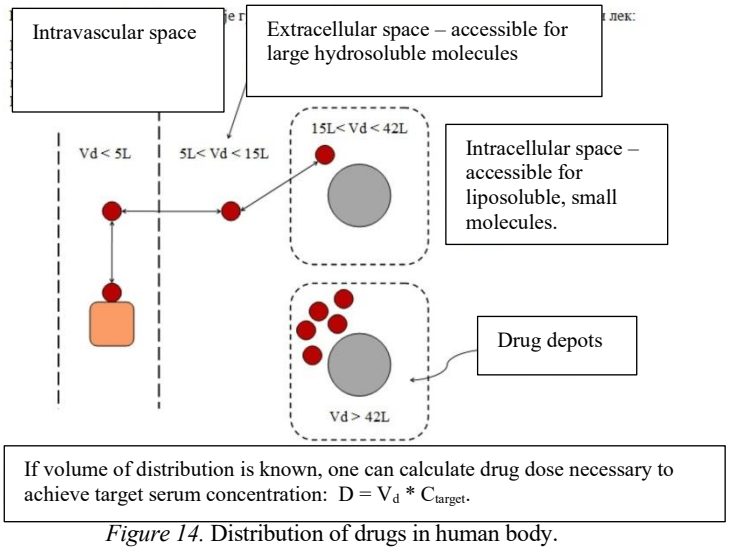


Figure 14. Distribution of drugs in human body.

It represents the volume in which the drug would be distributed under the condition that the drug concentration in all parts of that volume is the same, i.e., equal to the drug concentration in the blood. Although virtual, this quantity can tell us a lot about the behavior of the drug in the body. If Vd is about 5l, it can be assumed that the drug was distributed only in the intravascular space and could not leave the blood vessels (e.g. plasma expander dextran 70). If Vd is about 15L, it can be assumed that the drug was distributed within the extracellular fluid (because there is about 15L of it), that it is not liposoluble and that it does not penetrate inside the cells or into the CNS. If the volume of distribution is around 40L, the drug has penetrated all the cells of the body (Vd is equal to the volume of total water in the body), and if Vd is greater than 40L (sometimes several hundred liters), this means that the drug has been deposited somewhere in the body (the largest part of the drug dose is in the depot, the drug concentration in the blood is low, so the D/Cp ratio is high).

Biotransformation of drugs

When it comes to water-soluble drugs, they are relatively easily eliminated from the body. After filtration in the glomeruli of the kidneys, since they are mostly ionized, they remain in the lumen of the tubules and are excreted in the urine. This does not happen with liposoluble drugs. They are also filtered in the glomeruli, but from the lumen of the tubules they return to the blood again by freely diffusing through the membranes of the tubular cells. If nothing else were to happen to a liposoluble drug, once it is introduced into the body, it would remain there forever, without the possibility of being eliminated. It is for this reason that a defense mechanism was created during evolution that converts liposoluble substances into water-soluble ones and thus enables their elimination. Today, we call this mechanism of chemical change of the drug the process of biotransformation.

Biotransformation takes place mostly in the liver, on the smooth endoplasmic reticulum. There are a large number of enzymes that have very low specificity, so they can act on substrates of very diverse chemical structure. Among them, the most important are two compounds: cytochrome P450, which allows the insertion of an oxygen atom into the substrate molecule (thereby oxidizing it because the substrate gives up its electrons to oxygen) and cytochrome P450-reductase, which regenerates the oxidized cytochrome P450 and allows it to act on the next substrate molecule. Therefore, **oxidation** is the most common reaction in drug biotransformation. The oxidized drug now has an oxygen atom in its molecule that attracts electrons from the bond with hydrogen atoms; this ends with the dissociation of a hydrogen ion that is positively charged, while the drug molecule contains oxygen that carries one negative charge. The end result is the formation of an ionized, therefore water-soluble drug. The

oxidation process biotransforms catecholamines, neuroleptics, benzodiazepines and many other drugs. Although by far the largest number of drugs is oxidized under the action of cytochrome P450, some drugs (e.g., the antidepressants desipramine and nortriptyline) are affected by other oxidases of the endoplasmic reticulum or cytoplasm.

A smaller number of drugs are biotransformed by other types of chemical reactions. **Reduction** is the introduction of electrons into the drug molecule (reduction inactivates the venous vasodilator nitrates), and **hydrolysis** is the splitting of the drug molecule into two parts by the introduction of water molecules (e.g. hydrolysis of local anesthetics procaine, lidocaine, and others).

Sometimes these basic biotransformation reactions (oxidation, reduction, and hydrolysis), which are often called **first-phase reactions**, do not lead to the formation of a sufficiently ionized drug that would be easily eliminated from the body. Then it is necessary to add a polar radical to the already modified drug and increase its hydrophilicity. For this purpose, evolution has created enzymes that perform conjugation, i.e., the connection of modified drug molecules with polar radicals. The radicals that are most often "attached" to drug molecules are glucuronic acid, acetic acid, sulfate group, methyl group and amino acid glycine. For example, digoxin and paracetamol are conjugated with glucuronic acid, and sulfonamides and isoniazid are conjugated with acetic acid. We call **conjugation reactions phase II reactions** of biotransformation. Sometimes drugs do not undergo phase I reactions, but are directly conjugated with radicals. An example of this behavior is the opioid analgesic morphine, which is only conjugated with glucuronic acid..

Induction and inhibition of cytochrome P450. Both the number and activity of cytochrome P450 proteins can change depending on the presence of chemical substances in the human body. Some substances, by influencing gene expression, increase (**induce**) the synthesis and activity of this enzyme and thus accelerate their own biotransformation but also the biotransformation of other substances. Known inducers of cytochrome P450 are phenobarbital, carbamazepine, rifampicin, glucocorticoids, many toxins that pollute the human environment (polycyclic aromatic hydrocarbons from tobacco smoke or grilled food, dioxin, etc.) as well as plants from the *cruciferous family* (cabbage, kale, cauliflower, Brussels sprouts, broccoli) and St. John's wort. Other drugs **inhibit** the activity of cytochrome P450 by binding to its heme. These are: drugs containing the imidazole group (cimetidine, ketoconazole), erythromycin, estrogen ethinyl estradiol, spironolactone, chloramphenicol, norethindrone, anesthetic fluorescein, solvent carbon disulfide, propylthiouracil, grapefruit juice and other substances. Whether they are inducers or inhibitors of cytochrome P450, they can cause serious interactions with drugs that we use in practice. Inducers can accelerate the metabolism of a drug that a patient is taking chronically and lead to a drop in the concentration of that drug in the blood below the therapeutic level (and thus to the cessation of the drug's effect). This can sometimes be very dramatic and lead to serious consequences (for example, in patients with artificial heart valves who are on lifelong therapy with oral anticoagulants). On the other hand, inhibitors can lead to an increase in the concentration of other drugs in the blood to toxic levels. The best way to avoid such unpleasant drug interactions is to avoid unnecessary co-administration of multiple drugs or, when combination therapy is absolutely necessary, to reduce or increase the dose of the second drug when the first drug is an inhibitor or inducer of cytochrome P450.

Cytochrome P450 inhibition can be reversible (competitive) or irreversible (so-called **suicide inactivation**). In reversible inhibition, after the inhibitor leaves the enzyme, the enzyme remains active. In suicide inactivation, the inhibitor drug is itself metabolized by cytochrome P450, and converts to a form with reactive radicals, so that it then irreversibly binds to the enzyme. Such an enzyme remains permanently inactive, and its lost function can only be compensated for by the synthesis of a new enzyme. An example of a drug that causes suicide inactivation of cytochrome P450 is erythromycin.

There are multiple cytochrome P450 isoforms in each individual, with the most abundant being **CIP3A4** (28% of the total P450 content in the liver), **CIP2C9** (20%), **CIP1A2** (12%), **CIP2E1** (6%), **CIP2A6** (4%) and **CIP2D6** (4%). Some drugs are metabolized by multiple isoforms (e.g. paracetamol is metabolized by CIP3A4, CIP1A2 and CIP2E1), while some are metabolized by only one (e.g. ibuprofen by CIP2C9). Interestingly, the abundance of individual cytochrome P450 isoforms changes during the development of each individual. For example, the CIP3A7 isoform appears only during fetal life, and disappears after birth. *Drugs that are metabolized by multiple cytochrome isoforms are more suitable for clinical use than drugs that are metabolized by only one isoform*. If one of the isoforms is inhibited by another drug that is administered at the same time, the first drug will be metabolized more intensively via the intact isoforms, so its concentration in the blood will not increase significantly. In the case of drugs that are metabolized via only one cytochrome isoform, the possible inhibition of that isoform will lead to very high drug concentrations in the blood and the manifestation of toxic effects. Cytochrome P450 inducers and inhibitors are most often specific for individual isoforms, so to predict the effects of enzyme induction or inhibition, it is necessary to know two things: via which isoform(s) a drug is oxidized, and on which isoform(s) the inducer or inhibitor in question acts.

Elimination of drugs

Drug excretion is the process by which drugs are removed from the body's internal environment into the external environment.

Drug excretion in urine

The most important route of drug elimination from the body is through the kidneys. About 1200 ml of blood flows through both kidneys every minute, and of this, about 120 ml is separated in the glomeruli into the ultrafiltrate that flows further down the tubules. All drugs with a molecular weight of less than 60,000 Daltons are filtered in the glomeruli. If they are in an ionized state, they cannot diffuse through the tubule wall back into the blood, but remain in the lumen of the tubules and are eliminated in the urine. The extent to which a drug will be ionized depends primarily on its molecular structure and then on the pH of the tubular fluid. Liposoluble drugs (those that have few oxygen, nitrogen, or sulfur atoms) are minimally ionized regardless of the pH of the environment. However, most drugs are at least somewhat water-soluble, and can be considered weak acids or weak bases (e.g., drugs that have a COOH group are weak acids, and drugs that have an NH2 group are weak bases). If a drug is a weak acid, it will be more ionized (dissociated) the more basic the tubular fluid is (higher pH), which means that more of it will be excreted in the urine. On the other hand, if a drug is a weak base, it will be more ionized (dissociated) in acidic urine (low pH) and more will be excreted. By changing the pH of the urine, we can increase or decrease the excretion of a drug. For example, in poisoning with barbiturates or acetylsalicylic acid (both drugs are weak acids), the elimination of the poison can be accelerated by the administration of NaHCO3, which leads to alkalinization of the urine.

In addition to filtration, drugs can reach the lumen of the tubules (and thus the urine) by the process of secretion from tubular cells. Secretion takes place in the proximal tubule by means of two nonspecific transport systems, located in the luminal membrane of the tubulocyte. One system transports weak acids ("anionic" system) and the other weak bases ("cationic" system). Both systems transport endogenous substances under physiological conditions; for example, the anionic system transports uric acid. The capacity of these secretory systems is very large, so that drugs that undergo tubular secretion are eliminated very quickly. An example of this is penicillin (secreted by the anionic system), in which half of the administered dose is eliminated after 30 minutes. In addition to penicillin, many diuretics, indomethacin and salicylates are secreted by the anionic system. Atropine, morphine, neostigmine, quinine, cimetidine and other drugs are secreted into the urine by the cationic system.

Drugs that are secreted can interfere with the secretion of endogenous substances and thus cause adverse effects. Thus, diuretics (which use the anionic system) often cause hyperuricemia because they interfere with the secretion of uric acid.

Transport systems can be blocked and thus slow down the elimination of some drugs. Thus, probenecid blocks the anionic transport system and slows down the elimination of penicillin.

Tubular secretion is a very important mechanism for the excretion of drugs that are strongly bound to plasma proteins, because they can practically not be filtered in the glomeruli. This mechanism is much less developed in newborns and very old people.

Some natural substances and rare drugs can be actively reabsorbed in the tubules after filtration into primary urine, e.g., glucose, amino acids and ions. Uric acid is both actively reabsorbed and actively secreted, so it moves in both directions. With drugs called uricosurics (probenecid, sulfinpyrazone), we can block the active reabsorption of uric acid, and thus increase its excretion. On the other hand, the antituberculosis drug pyrazinamide blocks the tubular secretion of uric acid, and thus increases its concentration in the blood.

Excretion of drugs in bile

In addition to urine, drugs can also be eliminated via the bile. In quantitative terms, excretion via the bile is of little importance for most drugs. However, the presence of a drug in the bile can have therapeutic significance; for example, antibiotics that are excreted in the bile can be usefully used to treat biliary bacterial infections (ampicillin, ceftriaxone, rifampicin). Rare drugs that are almost entirely excreted via the bile can be used safely in patients with impaired renal function. These include the cardiotonic digitoxin, the tetracycline doxycycline, the opioid morphine, and others. Although drugs can reach the bile by diffusion, this mechanism of excretion is less significant, because it cannot concentrate the drug in the bile, the total daily volume of which is not excessively large (about 1.5 L). From the hepatic sinusoids, drugs enter the hepatocytes via the basolateral membrane using transporters from the superfamily of “solute carriers”.

Hepatocytes have at least three active transport systems on their membrane facing the bile ducts, which release drugs into the bile. Two of the three active biliary secretion systems are very similar to the anionic and cationic tubular secretion systems in the kidneys, while the third system is a unidirectional drug efflux pump that uses ATP (called the ATP-binding cassette, or abbreviated ABC). Active biliary secretion systems are designed to first excrete drugs that have been previously conjugated with glucuronic acid or some other radical. As with renal tubular secretion, it has been observed that newborns and the very elderly have reduced activity of the transport systems in the bile ducts. Liver disease can also impair active biliary secretion systems, thereby slowing the elimination of some drugs that use these systems, such as probenecid, diethylstilbestrol, and digoxin.

An additional problem with biliary excretion of drugs is the possibility that they may be reabsorbed in the small intestine, i.e., undergo enterohepatic recirculation. An example of a drug that is reabsorbed in the small intestine after being excreted in the bile is the antibiotic chloramphenicol.

Elimination of drugs in exhaled air

Gases and highly volatile substances are eliminated through the lungs and exhaled air. Elimination is by simple diffusion, and there are no specialized transport systems. Anesthetic gases and vapors are taken in and eliminated through the lungs. A small portion of ingested alcohols (ethyl alcohol, methanol, ethylene glycol) is also eliminated through the lungs. Increasing the rate and depth of respiration can increase the elimination of these substances to some extent.

Gases, vapors, and other substances that are poorly soluble in the blood are eliminated rapidly through the lungs (e.g., nitrous oxide, N_2O), while highly soluble substances are eliminated very slowly (e.g., halothane, ethanol).

Excretion of drugs in saliva, sweat, sebum, and tears

Almost all drugs can be found in saliva, sweat, sebum, and tears; the amount of drug that can be eliminated by these routes is negligible. These routes of elimination may only be of diagnostic significance because drug concentrations in these fluids directly correlate with blood concentrations. Also, the bitter taste that patients sometimes complain of after intravenous injection is thought to result from the rapid excretion of the drug in saliva.

Excretion of drugs in milk

Most drugs taken by the mother pass into the milk. The concentration of the drug achieved in the milk depends primarily on the concentration of the drug in the mother's blood, its liposolubility, binding to plasma proteins (high binding means lower excretion in milk) and the existence of an active secretion mechanism. Milk is slightly acidic (pH 7.2), so drugs - weak bases - accumulate somewhat more in it.

Drugs with a high affinity for the milk protein lactalbumin can be concentrated in milk, then liposolubil drugs that dissolve in milk fats, and drugs that act as chelating agents, i.e., bind calcium from milk (e.g., antibiotics tetracyclines).

When the mother takes a drug, she should avoid breastfeeding immediately after taking the drug, because then the largest amount of the drug is in the milk. Fat-soluble drugs will be more present in the breast milk of the infant if the feeding is in the morning and if the feeding lasts longer, because then the fat content in the milk is higher. As a rule, drugs with a shorter half-life should be used, because then the infant's exposure to the drug through the milk will be lower than when taking drugs that are eliminated slowly.

It is very important to know when the mother is taking a drug, what percentage of the dose she took (in mg/kg/day) the breastfed child will ingest through the milk (also converted to mg/kg/day). This percentage is called the relative dose for the infant, and if it is greater than 10%, the possibility that the drug will exert pharmacological effects in the infant is high, so either breastfeeding should be avoided, or the child must be monitored closely for the appearance of possible side effects of the drug.

Pharmacokinetic parameters of elimination of drugs

The mathematical quantities that tell us about the rate of drug elimination from the body are clearance (CL), elimination constant (Ke), and half-life ($T_{1/2}$). All three quantities can be calculated from the curve that describes serum concentration of the drug over time (see figure)..

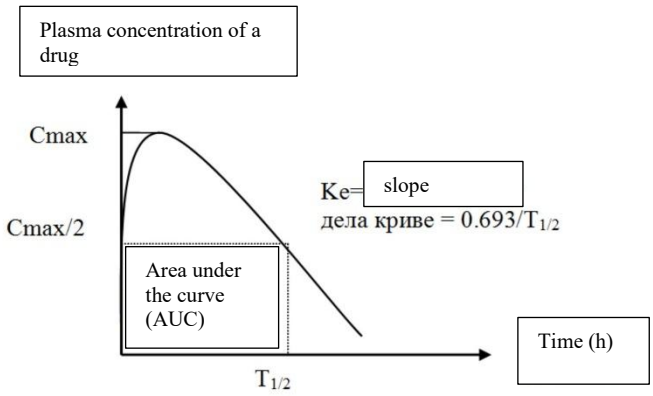


Figure 15. Blood drug concentration after a single oral dose.

Drug clearance is the amount of drug cleared from blood plasma per unit of time. Total drug clearance includes all elimination pathways and can be expressed as the sum of renal, hepatic, pulmonary, and other clearances. It is calculated as the quotient of the total amount of drug eliminated per unit of time and the plasma drug concentration. In practice, total drug clearance is determined from the serum drug concentration/time curve (see figure above), as the quotient of the drug dose and the area under the curve (AUC). If we wanted to calculate only the renal clearance of a drug, then the total amount of drug excreted via the kidneys per unit of time would be divided by the area under the curve. The half-life ($T_{1/2}$) is the time it takes for half of the administered drug to be eliminated from the body. In practice, the half-life is determined from the serum drug concentration/time graph, by reading the time required for the drug concentration on the descending part of the curve to decrease by half. It is clear that the slope of the descending part of the curve actually determines the rate of elimination: the higher the slope, the faster the elimination, and vice versa. The slope is mathematically expressed as the tangent of the angle at which the descending part of the curve is inclined relative to the x-axis, and is also called the drug elimination constant (Ke). There is a simple mathematical relationship between the elimination constant (slope of the curve) and the half-life: T1/2 = 0.693/Ke.

Most drugs are eliminated according to so-called **first-order kinetics** (or linear kinetics, which is a synonym). This means that the rate of elimination is higher the higher the concentration of the drug in the blood. Some drugs are metabolized by enzymes whose total number is small, i.e., the total capacity for elimination is limited. At lower blood concentrations, such drugs are also eliminated according to first-order kinetics; however, at higher concentrations, the enzymes that perform elimination become saturated so that the increase in the drug concentration in the blood is not accompanied by an adequate increase in the elimination rate. We say that this type of elimination is carried out according to **saturation kinetics**. Saturated elimination kinetics are observed for ethanol, phenytoin, fluoxetine, acetylsalicylic acid, dicumarol, and others. If drugs with saturation kinetics are overdosed, the elimination pathways (enzymes) are immediately completely saturated, so that the same amount of drug is always eliminated per unit of time - the same as the capacity of the enzymes that perform elimination. Then we say that saturation kinetics transitions to the so-called **zero-order kinetics**.

Steady-state

When it comes to drugs with first-order kinetics, after repeated administration of the same dose, an steady-state is established in which the amount of drug eliminated between two doses of the drug is equal to that dose. After the first dose, only part of the dose is eliminated in the dose interval, so that the next dose significantly increases the drug concentration in the blood. The increased drug concentration in the blood leads to an acceleration of elimination, so that in the second dose interval a larger part of the dose is eliminated than in the first. The third dose of the drug further increases the drug concentration in the blood, so that in the third dose interval an even larger part of the dose is eliminated. After 4-5 dose intervals (provided that they are approximately equal to the drug elimination half-life), an steady-state is established. Then the drug concentration in the blood is maintained at a constant level, oscillating around a certain value. In practice, our goal is to achieve a steady state by administering the drug to the patient at regular intervals (dose intervals) in which the concentration of the drug in the blood is high enough to exert the therapeutic effect of the drug, but not too high so as not to exert the toxic effects of the drug..

Steady state can be reached faster than 4-5 half-lives if we apply a loading dose of the drug that is several times higher than the usual single dose (maintenance dose). We do this, for example, when we apply a loading dose of the cardiotonic digoxin, followed by maintenance doses (such a procedure is called "rapid digitalization"). When applying the loading dose, the doctor should be careful and calculate it well, because it is easy to overdose it and cause serious side effects.

For successful therapy, it is very important that the patient takes their medication regularly, i.e., not to miss a single dose. If this happens, the equilibrium state is disturbed and the concentration of the drug in the blood falls. It is necessary to pass several dose intervals to re-establish the original steady-state with the desired concentration of the drug in the blood.

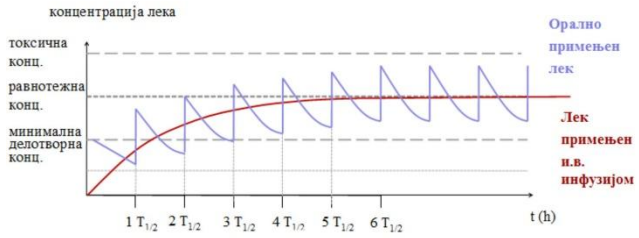


Figure 16. Steady state establishment after chronic drug use

In multiple-dose administration, if the dosing interval is similar to $T_{1/2}$, after establishing the steady-state, the amount of drug eliminated between two doses is equal to the administered dose of the drug. The concentration of the drug in the blood reaches maximum values soon after drug intake, then decreases during the dosing interval to minimum values (immediately before the administration of the next dose), i.e., it fluctuates around the average, steady-state concentration.

By properly selecting the dose and dosing regimen, a constant average (steady-state) concentration of the drug in the blood is achieved, with maximum concentrations (peaks) lower than toxic and minimum concentrations that are still effective.

DRUGS AND FOOD

For oral administration of drugs, it is useful to know the possible effects of food and its ingredients on the drug itself. These effects can be classified into two large groups: effects on pharmacokinetics and effects on the drug's action.

Pharmacokinetic effects are particularly numerous in the drug absorption phase. Every type of food (especially fatty foods) slows down gastric emptying. After food is ingested, it takes about 2-3 hours for it to pass into the stomach. If the patient takes the drug immediately after a meal, this means that it will only completely reach the small intestine after 2-3 hours, which significantly slows down the absorption of the drug. For most drugs that are used for a long time (e.g. for months), the speed of drug absorption is not important; but if we want a quick effect of the drug (e.g. an antihypertensive in a hypertensive crisis), then it should definitely be given before a meal, i.e. on an empty stomach.

On the other hand, taking the drug immediately after a meal, i.e. on a full stomach, can significantly affect the degree of drug absorption. Some drugs are better absorbed by fat from food, because it stimulates the secretion of bile acids, which facilitate the dissolution of the drug in the lumen of the small intestine, thereby increasing its absorption. Other drugs are converted by stomach acid into a form that is better absorbed. The group of such drugs that should be taken on a full stomach includes: carbamazepine, griseofulvin, saquinavir, tacrolimus, isotretinoin (due to easier dissolution), itraconazole, ketoconazole and amprenavir (due to the positive effect of stomach acid).

There are also drugs for which food ingredients interfere with absorption. Some are not stable in an acidic environment, so they are broken down under the influence of gastric juice. These are primarily antimicrobial drugs: ampicillin, azithromycin, isoniazid, penicillin V and erythromycin. The second group of drugs, which are chelated (bound) with metal cations (calcium, magnesium, iron, etc.) and are thus less well absorbed, includes: bisphosphonates, penicillamine, tetracyclines and quinolone antibiotics. To improve the absorption of such drugs, the patient should take them at least one hour before or at least 2 hours after a meal.

Certain types of food can affect the metabolism of drugs. Ingredients in grapefruit juice inhibit the metabolism and transport of some drugs before they reach the systemic circulation, thereby increasing the concentration of these drugs in the blood (and thus their effect). If grapefruit juice is taken for several days, its effects on drugs last for several weeks. Therefore, grapefruit juice

should be avoided if you are taking any of the following medications: amiodarone, statins, cyclosporine, calcium channel blockers, benzodiazepines, saquinavir, and sildenafil. As previously mentioned, orange juice and apple juice interfere with the absorption of fexofenadine and other medications that use the OATP2B1 transporter in the intestinal mucosa.

Some foods contain ingredients that affect the effects of medications. For example, foods high in protein can interfere with the passage of levodopa across the blood-brain barrier (because amino acids from food compete with levodopa for the transporter), which reduces the effect of levodopa in Parkinson's disease. Another classic example is foods rich in tyramine (aged cheese, smoked fish and yeast), which can trigger a hypertensive crisis in patients on long-term monoamine oxidase inhibitor therapy (see chapter on antidepressants). Another example is relevant for clinical practice: the use of large amounts of potassium-rich foods (e.g. tomato juice) should be avoided in patients taking drugs that interfere with renal potassium excretion (potassium-sparing diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), as hyperkalemia may occur. Finally, sometimes a drug should be taken with food to avoid irritation of the gastric mucosa (e.g. nonsteroidal anti-inflammatory drugs, metformin), or to prevent the occurrence of hypoglycemia (e.g. when taking oral hypoglycemics).

LIVER DISEASES AND DRUG METABOLISM

A large number of liver diseases impair the liver's ability to metabolize drugs. The degree of impairment of biotransformation function depends on the severity and stage of each disease. Slow drug metabolism is observed in cirrhosis, fatty liver, acute hepatitis of various etiologies, and hepatocellular carcinoma. Therefore, in such conditions, all drugs that are metabolized in the liver require a dose reduction. The extent to which the dose should be reduced depends on the degree of liver failure caused by the disease in the patient. Although there is still no adequate tool for assessing the degree of liver failure, we use the Child-Pugh classification into A, B, or C stages, with A being the mildest and C the most severe form of liver failure. Patients are classified into these stages according to albumin, bilirubin, prothrombin time, and the presence or absence of encephalopathy and ascites. The dose of drugs is adjusted only in stage B, when it should be reduced by 50%, and in stage C, when it should also be reduced by 50%, but also the dosage interval should be extended by 50%.

In cirrhosis of the liver (end-stage), the greatest effect of the disease is on drugs that undergo first-pass metabolism through the liver and are less bound to plasma proteins. Since collateral blood flow develops (via the esophageal and ano-rectal veins) due to the slowed blood flow through the portal circulation, most of the absorbed drug bypasses the liver and reaches the systemic circulation directly. Therefore, the bioavailability of such drugs increases, as does their concentration in the serum, and thus the intensity of the effect and the frequency of side effects. Thus, in cirrhosis of the liver, the bioavailability of labetalol, propranolol, pethidine and morphine becomes twice as high.

On the other hand, blood flow through the liver significantly affects the metabolism of drugs that are characterized by being metabolized very quickly in it. All conditions that reduce blood flow through the liver (e.g. heart and respiratory failure) will slow down the metabolism of such drugs (amitriptyline, imipramine, isoniazid, lidocaine, propranolol, verapamil, morphine, meperidine, pentazocine).

It is important to understand that kidney function is particularly compromised in cirrhosis of the liver, because blood is retained in the intestinal and gastric circulation, so kidney perfusion is impaired. This makes the kidneys sensitive to the effects of nephrotoxic drugs, which should be avoided, otherwise kidney failure may occur. Some of the drugs that should be avoided in patients with cirrhosis for this reason are: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and aminoglycosides.

KIDNEY FAILURE AND DRUGS

Patients with impaired renal function face several problems when using medications: 1) they excrete drugs and their metabolites slowly; 2) they become more sensitive than other people to the effects of some drugs; and 3) they have a harder time tolerating side effects of drugs. These problems can be reduced or avoided by using lower doses of drugs or by choosing the right drug. It is especially important to determine the right dose of a drug in people with renal insufficiency: it should not be too high or too low. When it comes to drugs that are largely metabolized to inactive metabolites, and then these same metabolites are only partially excreted via the kidneys, a dose reduction is not necessary in renal insufficiency. This is especially true for drugs with a

wide therapeutic index. On the other hand, drugs that have a narrow therapeutic index and are largely excreted unchanged in the urine or have active metabolites that are excreted in the urine require very precise dosing based on the patient's creatinine clearance, with occasional measurement of the drug's serum concentration.

How to use creatinine clearance to adjust maintenence drug doses in renal failure? In the following way:

First of all, we need to determine the fraction (F) of the drug that is excreted unchanged in the urine (e.g., for aminoglycosides, F=0.9, and for tetracyclines, F=0.5). Then, since the renal clearance of the drug is proportional to creatinine clearance, we need to find the ratio of creatinine clearance in a patient with normal creatinine clearance to whom we are giving the drug:

Creatine clearance in renal failure (ml/min) / 120 = K

Based on these two data (F and K), we calculate the factor (D) by which the usual dose of the drug should be multiplied to obtain the dose of the drug in our patient with renal failure:

$D = 1 - F + F \cdot K$

It is very important, however, that the initial (loading) dose of the drug (if included in the therapeutic regimen) in patients with renal insufficiency is not corrected by the aforementioned factor, but remains the same as in people with normal renal function.

In order not to calculate maintenence drug doses separately for each patient with renal insufficiency, tables with already calculated doses according to the categories of renal insufficiency are usually used in practice (stage 3 - creatinine clearance 30-59 ml/min, stage 4 - creatinine clearance 15-29 ml/min and stage 5 - creatinine clearance less than 15 ml/min). These tables are not entirely precise, but they can meet the needs of the majority of patients; they can usually be found in Summaries of Product Characteristics, or in manuals, such as the British "BNF" or our "Pharmacotherapy Manual", published by the Agency for Medicines and Medical Devices of Serbia.

Creatinine clearance can be estimated from serum creatinine concentration using the Cockcroft-Gault formula:

Creatine clearance = (((140 - age in years) x (weight in kg)) x 1.23) / (serum creatinine in micromol/l)

*for women, the result of the formula is multiplied by a factor of 0.85

HEART FAILURE AND DRUGS

Heart failure leads to edema of the gastrointestinal tract, which makes it difficult to absorb drugs. Therefore, sometimes the effect of orally administered drugs is absent, so the doctor must switch to parenteral administration.

On the other hand, heart failure reduces blood flow through the liver, so one can expect a weaker elimination of drugs that are otherwise rapidly metabolized in the liver (isoniazid, lidocaine, propranolol, morphine, pentazocine, pethidine), and an increase in their serum concentration. This is also contributed by a decrease in the function of cytochrome P450 oxidase.

In patients with heart failure, kidney function is particularly vulnerable, because it depends on blood flow, which is weakened in failure. Therefore, such patients should not be given drugs that inhibit prostaglandin synthesis (nonsteroidal anti-inflammatory drugs: acetylsalicylic acid, ibuprofen, diclofenac, and others), as they can further worsen renal blood flow (which is dependent on local prostaglandin synthesis), and seriously damage renal excretory function.

Interestingly, in a hospital setting, an abnormal increase in serum aminotransferases is most often a consequence of congestive heart failure, so such a laboratory abnormality should not be immediately attributed to the drugs that the patient is taking at the same time, just because these drugs are metabolized in the liver. Finally, a number of drugs can cause heart failure as a side effect. Such drugs include calcium channel blockers (except amlodipine and felodipine), oral antidiabetics from the thiazolidinedione group (pioglitazone and rosiglitazone weaken mitochondrial function in myocardial cells), nonsteroidal anti-inflammatory drugs (especially those that selectively inhibit cyclooxygenase 2 - leading to fluid retention and heart strain), cytostatics from the anthracycline group (doxorubicin - creates free radicals that damage the myocardium), etc.

DRUG ALLERGY

Any drug can cause an allergic reaction in patients, even those used to treat allergies. Of course, some drugs do this more often (e.g. penicillin), and some very rarely (e.g. lidocaine). The drug that causes an allergy actually acts as an antigen, either by itself or in conjunction with some component of the body (most often of a protein nature). After the first contact with the drug, the body's immune system creates free antibodies to the drug or clones of T-lymphocytes that can (via specific antibodies on their membrane) recognize the drug. Depending on the site (type of cells, tissue) to which the drug is attached and the dominant mode of reaction of the immune system (by creating free antibodies or T-lymphocytes), upon subsequent contact with the drug, the body can react allergically in 4 different ways (four types of allergic reaction):

1. type (anaphylactic reaction)

In this type of reaction, after the first contact with the drug, the organism produces IgE antibodies to the drug, which bind with their Fc part to the mast cell membrane. When the drug enters the organism the next time (at the earliest after 5-7 days from the first contact), it binds to the IgE antibodies on the mast cells and causes degranulation of these cells. A series of mediators are released from the mast cell granules (histamine, chemotactic factors, heparin, arylsulfatase B, etc.) that cause vasodilation, hypotension and edema (due to increased capillary permeability). Clinically, this can manifest as shock (so-called anaphylactic shock), swelling of the soft tissues of the neck and trachea that causes the patient to suffocate (Quincke's edema, i.e. angioedema) or bronchospasm. Milder reactions are manifested only by rash - urticaria (hives). Type I allergic reactions occur within minutes to hours of re-exposure to the drug.

Anaphylactic reactions are treated by stopping the drug that caused it and then immediately administering adrenaline (0.5 mg subcutaneously or 0.3 mg intramuscularly or 0.2 mg intravenously). Since adrenaline has already been administered, the patient should be given an injection of corticosteroids and H1 and H2 antihistamines. If the anaphylactic reaction is manifested only by hives, then only H1 antihistamines are sufficient.

2. type (direct cytotoxicity)

In a type 2 reaction, after the first exposure to a drug, the immune system produces IgG or IgM antibodies to the drug. When the drug is reintroduced into the body, it binds to the membrane of a type of blood cell. The antibodies then bind to the drug and activate complement, which destroys the membrane of the blood cell. The result is cell lysis, i.e., hemolytic anemia, leukopenia, or thrombocytopenia, depending on the type of cell to which the drug is bound. The time between reexposure to the drug and the onset of a type 2 allergic reaction varies greatly from patient to patient.

3. type (creation of immune complexes)

In this type of reaction, the body also produces IgG or IgM antibodies, but the drug does not bind to the cell membrane. First, with repeated administration of the drug, the drug and the antibody bind (i.e., so-called immune complexes are formed), and then the antigen-antibody complexes are deposited in the tissues and walls of blood vessels. These complexes in the tissues cause the activation of complement and inflammatory cells (lymphocytes, polymorphonuclear cells, macrophages) and the development of inflammation. This type of drug allergy can manifest as serum sickness, vasculitis, rash, arthralgia and/or increased body temperature. The third type of allergy usually occurs 1-3 weeks after the patient is re-exposed to the drug.

4. type (delayed hypersensitivity)

Delayed hypersensitivity is related to the formation of T-lymphocyte clones that recognize the drug as an antigen. Since the immune response of T-lymphocytes takes some time, the reaction to the re-introduction of the antigen occurs only after a latent period of 48-72 hours, sometimes only after 7 days. Hence the name delayed hypersensitivity. Contact dermatitis that can occur after topical application of drugs is based on the mechanism of delayed hypersensitivity. The same mechanism is used to cause allergic hepatitis and nephritis after drug administration.

Cross-allergy

Drugs with similar chemical structures can cause the same allergic reaction even though only one of them has previously come into contact with the body. Because of their similar chemical structure, the immune system recognizes them as the same substance, the same antigen, and therefore an allergic reaction occurs. The best-known example of cross-allergy is penicillins and cephalosporins. A person who is allergic to penicillin can also have an allergic reaction to cephalosporins (about 8-15% of patients), even though they have never received this type of antibiotic before. Namely, penicillins and cephalosporins have one identical part of the molecule - the beta-lactam ring - which is why the immune system recognizes them as the same type of antigen. In addition to penicillins, cross-allergy has also been recorded between vancomycin and teicoplanin, within the group of aminoglycoside antibiotics, as well as between certain nonsteroidal anti-inflammatory drugs.

The most frequent manifestations of drug allergy

Drug allergy most often manifests itself on the skin, as a maculo-papular rash (e.g., with allopurinol, beta-lactams, antiepileptics), urticaria (e.g., with antibiotics, antiepileptics, ACE inhibitors, neuromuscular blockers, nonsteroidal anti-inflammatory drugs), Stevens-Johnson syndrome (blisters on the mucous membranes and skin, e.g., with sulfonamides, allopurinol, antiepileptics, oxicams, corticosteroids, pantoprazole, tramadol) or the so-called fixed eruption, i.e. the appearance of hyperpigmentation always in the same place after repeated exposure to the drug (tetracyclines, sulfonamides, nonsteroidal anti-inflammatory drugs, antiepileptics). In addition to the skin, internal organs can also be affected in drug allergies, resulting in hepatitis, nephritis, hemolytic anemia, thrombocytopenia, leukopenia, or vasculitis. Finally, sometimes drug allergy manifests itself as a syndrome, such as: serum sickness (skin rash, arthralgia, and fever, e.g., with the use of heterologous antibodies, infliximab, allopurinol, thiazides), DRESS syndrome (skin rash, fever, eosinophilia, lymphadenopathy, liver damage, e.g., with sulfonamides, allopurinol, antiepileptics) or lupus erythematosus-like syndrome (e.g., with hydralazine, procainamide, isoniazid, drugs that block the effect of tumor necrosis factor alpha).

Procedure with a patient allergic to a drug

When we determine that a patient is allergic to a drug by skin tests (prick and intradermal tests can determine type 1 allergies, patch tests can determine type 4 allergies), by measuring specific IgE antibodies in plasma, or by Coombs' test (type 2 allergies), we should first discontinue further use of that drug, and then advise the patient to avoid re-use of the same drug in the future. If there is a drug with the same or similar effect as the one that caused the allergy, but with a different chemical structure (so that there is no risk of cross-allergy), the patient should be given such a drug in the future. If there is no alternative medicine, and the patient's condition requires therapy with the drug that caused the allergy (otherwise his life will be at risk), we can continue the therapy using the desensitization procedure, which induces a state of temporary tolerance to the drug. In the past, the desensitization procedure was carried out through intracutaneous and subcutaneous administration of the drug, but today it is carried out intravenously. First, at least 4 dilutions of the drug should be made (1:10, 1:100, 1:10.00 and 1:10,000), and then, with premedication with corticosteroids and antihistamines, start with the administration of a very small volume of the highest dilution. Then, 4 times, with intervals of about thirty minutes, increasingly larger volumes of the same dilution are administered. Then, the next highest dilution is administered, and so on, until the full dose of the drug is finally administered. Temporary tolerance will last as long as the drug therapy continues, and during that time the desensitization procedure should not be repeated. If, after a certain period of time after discontinuation of therapy, such a drug needs to be administered again, the entire desensitization procedure is repeated.

ELDERLY AND DRUGS

The use of drugs in the elderly (over 65 years of age) has certain characteristics that should be observed in order to avoid significant adverse effects. The characteristics may be related to the pharmacokinetics or pharmacodynamics of drugs.

When it comes to pharmacokinetic characteristics in the elderly, they exist in all phases – absorption, distribution, biotransformation and excretion of drugs. In the elderly, the absorption of drugs is not significantly reduced in quantitative terms; it may only be slowed down, due to slower gastric emptying (as a consequence of the decline of the autonomic nervous system).

Therefore, it is not necessary to change the dose of drugs due to changes in absorption. However, in the case of drugs that undergo metabolism during the first pass through the liver (e.g., propranolol), due to reduced blood flow through the liver in the elderly, the intensity of metabolism may be reduced, so the drug reaches higher concentrations in the blood after oral administration.

The distribution of drugs in the elderly is affected by changes in the composition of body fluids and tissues. Adipose tissue makes up a larger percentage of body mass than in youth: in men it increases from 18 to 36%, and in women from 36 to 48%. As a result, the volume of distribution of liposoluble drugs increases, which results in their longer retention in the body of an elderly person. This is especially important for psychotropic drugs. Longer retention of psychotropic drugs leads to a prolongation of their action.

The water content in the body of an elderly person decreases on average by 15%, which results in a decrease in the volume of distribution of hydrophilic drugs and an increase in their concentration in the blood. This has been observed with the use of most antibiotics, lithium and cimetidine.

The decrease in muscle mass in the elderly affects the decrease in the volume of distribution of drugs that bind to the muscles, such as, for example, digoxin. This increases the concentration of such drugs in the blood, and their effect on target tissues.

Due to the reduced concentration of albumin in the serum of elderly people (by as much as 25%), drugs that are highly bound to albumin will have a larger free fraction than in young people. This will make their effect more pronounced, so their dosage should be reduced proportionally. Examples of such drugs are: warfarin, pethidine, phenytoin and digoxin.

With age, the capacity of enzymes that catalyze the reactions of biotransformation of the first phase (primarily oxidation enzymes) decreases in the liver, while the capacity for conjugation reactions does not change. Also, in elderly people, blood flow through the liver decreases, which further slows down the metabolism of a number of drugs. The consequence of these changes is a significant prolongation of the half-life of some drugs, which means that their dosage should be reduced. An extreme example of such drugs are benzodiazepines (primarily diazepam), whose half-life is extended by as much as 2-4 times! Another important example is the cardiotonic digoxin, whose half-life is prolonged from 52 to 73 hours in the elderly.

Finally, the excretory capacity of the kidneys of the elderly is significantly reduced. Starting at the age of 36, creatinine clearance decreases by 1% each year; this means that, say, a 70-year-old person has a 35% lower creatinine clearance than a young person. This further means that the dose of those drugs that are eliminated via the kidneys should be reduced by as many percentages as the patient turns forty. The following table lists drugs whose dose should be reduced by a certain percentage in the elderly, because they are eliminated via the kidneys.

When it comes to the action of drugs (pharmacodynamics), the elderly are particularly sensitive to substances that have an effect on the central nervous system. Therefore, they should reduce the doses of psychotropic drugs, especially those with sedative effects (benzodiazepines, barbiturates, tricyclic antidepressants). Drugs that otherwise have adverse effects on the central nervous system, these effects are more common in the elderly (e.g., cardiotonic glycosides more often lead to psychotic reactions in the elderly).

MEDICINES WHOSE DOSE NEEDS TO BE ADJUSTED IN ELDERLY PEOPLE, BECAUSE THEY ARE ELIMINATED VIA THE KIDNEYS		
Acyclovir	Amiloride	Captopril
Atropine	Baclofen	Cyprofloxacin
Chlorpropamide	Chloroquine	Penicillins
Enalapril	Digoxine	Tetracycline
Furosemide	Ethambutol	Cephalosporins
Methotrexate	Midazolam	Metformine
Nitrofurantoin	Ranitidine	Procainamide
Triamterene	Aminoglycosides	Thiazide diuretics

Due to the almost regular presence of coronary artery atherosclerosis, the elderly are more sensitive to drugs that have a positive inotropic, hypertensive, hypotensive (a sudden drop in pressure leads to poor myocardial perfusion and infarction) or arrhythmogenic effect. Thus, many deaths of people over 45 years of age from myocardial infarction due to excessive use of aerosols with adrenergic beta-receptor agonists (e.g. orciprenaline) during asthma attacks have been described. On the other hand, the elderly are particularly sensitive to the negative inotropic effect of beta-blockers.

Adverse drug effects are more common in the elderly. Statistics show that serious adverse effects (those leading to hospitalization or death) are twice as common in the elderly as in those under 40 years of age. In particular, a higher incidence of colitis after antibiotic use has been observed. The most likely cause of the higher incidence of adverse effects is the significantly greater use of medications in the elderly.

To avoid adverse and toxic effects of drugs in the elderly, doctors should adhere to certain principles in the use of drugs:

- prescribe drugs to the elderly only if it is really necessary, and if you know their pharmacokinetics in the elderly well;
- prescribe as few drugs as possible;
- prescribe the lowest recommended doses of drugs;
- after the introduction of a new drug, monitor the patient frequently;
- always keep in mind that many drugs can weaken the cognitive functions of elderly patients, and sometimes even cause delirium;
- do not prescribe drugs to the elderly that are on the list created by the Canadian Beers in the twentieth century, which was later internationally recognized and is updated every 2 years. This list includes drugs whose use in the elderly does more harm than good (available on the website of the American Geriatrics Society).

CHILDREN AND DRUGS

When it comes to administering medications to children, it is important to understand that there are significant differences in pharmacokinetics and pharmacodynamics at different stages of a child's development. In popular terms, children are not small adults, infants (from 2 months of age to the end of the 1st year) are not small children, newborns (from birth to the end of the 1st month) are not small infants, and premature infants are not small newborns. Premature infants have only 10% of the glomerular filtration rate of a newborn, and glucuronidation processes are extremely underdeveloped. However, many functions are also underdeveloped in newborns (glomerular filtration rate is only 50% of the adult value), and only by the middle of the 1st year of life do they develop to a level that corresponds to the functions of an adult.

Children are particularly sensitive to drugs during the first year of life, due to slow elimination. On the other hand, from 2 to 12 years of age, drug clearance in children is higher than in adults, and during puberty there is a sharp decrease in clearance to the values that adults have. Therefore, children in the period from 2 to 12 years of age often require higher doses of drugs per kilogram of body weight than adults.

Premature children, newborns and infants have a significantly higher percentage of water in their bodies than adults; they also have a reduced amount of adipose tissue and a reduced concentration of albumin in the plasma, which binds drugs less strongly than in adults. Due to the higher percentage of water, the volume of distribution of many drugs is higher, so it is necessary to start therapy with a loading dose. However, the loading dose should be carefully determined, because due to the lower binding of drugs to albumin, the concentration of free drug in the plasma can increase to toxic levels.

Premature infants and newborns should not be given intramuscular injections, because due to poorly developed musculature, drug absorption from the injection site is unpredictable.

Premature infants have extremely thin skin, through which drugs are absorbed much more rapidly than in newborns. Cases of cyanosis in premature infants have been described due to aniline dyes on hospital bedding, which were absorbed through the skin and caused methemoglobinemia.

The effects of some medications are specific in childhood. Barbiturates and antihistamines (which have a sedative effect in adults) cause excitation and hyperactivity in children. Chronic phenobarbitone therapy interferes with learning and normal behavior in children; chronic corticosteroid therapy slows their growth. Antidepressants should be used with great caution in adolescents: a higher incidence of suicide has been observed than in adults using these drugs. Due to all these specificities, drug doses in children should be adjusted to age and body weight. Although there are formulas for calculating doses for children derived from adult doses based on body weight (Clark's formula: Dchild = Dadult x BW/70) or the child's age (Jung's formula: Dchild = Dadult x Age/(Age+12)), they are not reliable enough for routine use and tend to underdose the drugs. The safest way to choose dose is to use empirical doses for each child's age, determined through long-term pediatric practice in most countries.

A certain number of drugs are contraindicated for use in children. These are:

• tetracyclines (because they are deposited in bones and teeth during growth; teeth become yellowish, enamel is hypoplastic)

• quinolone antibiotics and uroantiseptics (pipemidic acid, ciprofloxacin, olfloxacin and others are not used in people under 17 years of age because they interfere with the development of articular cartilage)

• acetylsalicylic acid (in children under 8 years of age who have a viral infection, the use of aspirin carries a high risk of Reye's syndrome - hepatorenal insufficiency)

• chloramphenicol is relatively contraindicated in newborns. Namely, it can be used provided that its serum concentrations are controlled. If this is not possible, due to the immaturity of the enzymes that conjugate chloramphenicol in the liver, this drug may

accumulate in the newborn's body (because it is difficult to accurately dose the drug) and make damage to vital organs (kidneys, liver, heart) manifested by the deadly "gray baby syndrome" (anemia and cardiovascular collapse).

Some drugs in children have specific side effects that you should be aware of:
• furosemide can cause nephrocalcinosis;
• indomethacin can cause kidney failure or intestinal perforation;
• phenytoin causes skull thickening and coarse facial features;
• valproate can cause hepatotoxicity in children under two years of age;
• ceftriaxone in infants may lead to the formation of precipitates in the gallbladder (calcium-ceftriaxone), because in the bile it reaches concentrations above the threshold values for the onset of crystallization; these precipitates disappear spontaneously after cessation of ceftriaxone administration.

Many medicines do not have approved indications for children, because clinical studies on children have not been conducted, so drug manufacturers avoid applying to the competent state authorities for indications in children. This includes various oral forms of medicines, which are not adapted to children. Since there is a real need, such medicines are still given to children outside the indication area (out of label), but then the doctor who prescribes the therapy is responsible for all possible adverse effects. In children, it is primarily recommended to use liquid forms of medicines orally, because younger children often cannot swallow tablets or capsules, and there is a risk of aspiration. When there are no liquid forms of medicines on the market, a pharmacist can make a powder from a tablet or capsule, which is then mixed with a constituent (a pharmacologically inert substance) and divided into individual doses. Individual doses in powder form can then be mixed with a liquid and given to the child without the risk of aspiration. This method of preparing powdered doses for children from solid adult dosage forms is called ***trituration***. The safest recommendations for dosing individual drugs in children outside approved indications and dosage forms are found in the book British National Formulary for Children. This book can be easily obtained through book import companies or by purchasing online.

DRUGS AND FEMALES

Outside of pregnancy, the female sex differs little from the male sex in terms of pharmacotherapy. It has been observed so far that the renal clearance of drugs in women is about 10% lower than in men. Women are more sensitive to ethanol after oral use because alcohol is metabolized very little in their stomach wall; in men, a significant part of the ingested ethanol is already broken down in the stomach wall under the action of gastric alcohol dehydrogenase. In addition, it has been observed that women have lower gastric acidity and that their stomach empties more slowly; also, estrogens have a dual effect on cytochromes: they reduce the activity of CIP 2C19 in the liver, so the metabolism of some drugs may be somewhat slower, but they increase the activity of cytochrome CIP 2A6 and accelerate the metabolism of drugs that are substrates of this cytochrome isoform, e.g. nicotine. The above-mentioned changes in drug metabolism are much more pronounced in pregnancy, when estrogen concentrations in the blood are much higher.

The real specificity of women in terms of drug therapy occurs during pregnancy and lactation. First of all, the conditions under which the movement of the drug in the body changes. The motility of the gastrointestinal tract is slowed down compared to the state before pregnancy. The amount of body water increases by 8 liters, and blood flow in the skin also increases. The volume of blood plasma increases, and the concentration of albumin decreases by up to 10 grams per liter. Due to the high concentration of estrogen and progesterone in the blood, the clearance of some drugs increases; for example, in order to maintain therapeutic concentrations in the blood, it is necessary to increase the dose of antiepileptic drugs in the second half of pregnancy.

From the third month of pregnancy, the metabolism of drugs that the mother has taken into her body begins in the fetal liver. Since drugs are excreted into the amniotic fluid after being metabolized in the fetal liver and then ingested by the fetus, there is a tendency for some drugs to accumulate in fetal tissues. This has been shown to occur for penicillins, cephalosporins, and antiretroviral drugs, but the consequences of this phenomenon are unknown.

The placenta does not represent a significant barrier to the passage of drugs; practically, it can be considered that every drug that the mother takes also reaches the bloodstream of the fetus. During the first two weeks after fertilization, drugs either lead to the death and elimination of the embryo or (if the embryo survives) do not leave any consequences on the fetus. In the next 10 weeks of pregnancy (the first trimester), a number of drugs (which we call teratogenic) can cause disorders in the development of the fetus that manifest at birth as malformations (so-called congenital malformations). Therefore, these 10 weeks are the riskiest

period in the development of the fetus. In the second two trimesters of pregnancy, some drugs can have a toxic effect on the tissues of the fetus and lead to minor (microscopic and functional) damage, usually of the CNS and the eye (because their development takes place throughout the pregnancy). Because of all that has been said, every doctor should know which drugs can and cannot be used during pregnancy. Detailed tables with recommendations for the use of drugs in pregnancy can be found in publications of the Medicines Agency (e.g. in the "Pharmacotherapy Guide") or in the British National Formulary (BNF), which doctors should obtain every two to three years. However, drugs that certainly have a very pronounced teratogenic or fetotoxic potential are: ACE inhibitors and angiotensin receptor blockers, cytostatics, antiepileptics, coumarins and lithium.

The harmful effects of drugs on the fetus are subject to certain principles: (1) there is a dose-dependent harmful effect; (2) a drug can cause a harmful effect only at a certain stage of fetal development, when there is a receptor on which the drug will act; (3) the mechanism of action of the drug determines what kind of disorder will occur (for example, there are 18 basic signaling pathways that are important for organ development in both animals and humans).

When it comes to lactation, the problem is somewhat different. A certain number of drugs that are very polar (e.g. aminoglycosides) penetrate poorly into milk, so they can be administered to the mother during lactation. Most drugs, however, reach the milk in significant amounts; many liposoluble drugs in milk reach the same concentration as in plasma (antidepressants, for example) or even become concentrated in it. Given that the pH of milk is about 7.2, those drugs that are weak bases will also be concentrated in it. Drugs with a smaller volume of distribution, which are less bound to plasma proteins, pass more into milk. Among the drugs that penetrate into milk to a large extent, the following stand out: lithium, methimazole, iodine, sotalol, atenolol and others. Detailed tables with recommendations for the use of drugs during lactation can also be found in the above-mentioned publications.

INTRODUCTION OF NEW DRUGS TO CLINICAL PRACTICE

The development of a new drug is a very expensive and time-consuming process. The average duration of drug development is about 8 years, while the costs are around 800 million dollars. Before a newly synthesized drug is introduced into practice, it must go through several phases that often last several years. First of all, the drug must be tested on animals. It is necessary to examine the effects of the drug in vivo and in vitro, and its pharmacokinetics in animals. Several groups of animals should be exposed to large doses of the drug in order to determine its acute toxic effects - these are the so-called acute toxicity studies. Other groups of animals are exposed to the test drug over a long period of time in order to observe possible chronic toxic effects (chronic toxicity studies). Due to the significant differences in biochemical mechanisms between animals and humans, it is necessary to conduct these types of experiments on at least two different species, one of which is not a rodent (most often dogs or monkeys).

A new drug should also be tested on pregnant animals, in order to check whether there is a tendency to cause malformations in the offspring, i.e,. to see if the drug is teratogenic. Since microorganisms grow rapidly (a new generation of bacteria is formed every 30 minutes), their cultures are exposed to the drug in order to determine its mutagenic potential, i.e., the frequency of mutations in each subsequent bacterial generation. It is also necessary to examine the effect of the drug on reproductive functions in animals, so that it is given to at least two generations without interruption and the number and vitality of the offspring are monitored; these are reproductive toxicity studies. Finally, it is necessary to determine the carcinogenic potential of the new drug: its ability to cause malignant tumors in experimental animals.

Only after all animal tests have been conducted and approval has been obtained from an independent Ethics Committee can clinical trials of drugs be initiated. Clinical trials are conducted in 4 phases:

1. phase: The drug is administered to a small number of healthy volunteers to determine its pharmacokinetics (absorption, distribution, biotransformation, and elimination) in the human body.

2. phase: A drug is given to a small group of patients to determine its effectiveness in controlling the disease for which it is suspected to be effective. In this phase, the drug is usually given in several different doses to determine whether there is a dose-dependent effect and which dose has the best efficacy..

3. phase: This phase can only be approached if the drug has shown satisfactory efficacy in the previous phase. The drug is now given to a large number of patients who have been selected by random selection. The effects of the new drug in these patients are compared with the effects of the previously used treatment method in another group of patients (e.g. with the most effective drug to date), as well as with the natural course of the disease in a third group of patients who are without therapy, i.e. receive only a placebo (a placebo is an indifferent substance /sucrose, starch, etc./ without pharmacological effect

that looks like the new drug, so that patients who take it believe that they are taking an effective drug). Sometimes the use of a placebo must be omitted for ethical reasons, because it is not justified to use it in patients who we know will progress during the study; in such cases, the new drug is compared only with the most effective drug to date. The comparison can be done using the so-called single-blind method, when the doctors conducting the study know which patients are receiving the new drug and which the old drug or placebo, while the patients do not. In order to achieve greater objectivity, whenever possible, the study should be conducted using the so-called double-blind method. In such a study, neither the doctors nor the patients know during the study which patients are receiving the new drug, which the old drug, and which the placebo. Only at the end of the study are sealed envelopes with codes that allow the classification of patients into groups opened. Sometimes clinical studies are planned according to the principle of "cross-over design": in the first period of the study, one group receives the drug being tested (the new drug), and the other receives a placebo (or the most effective drug to date, the so-called active comparator), and after the so-called After a "washout period" of several days or weeks, when patients no longer receive any of the drugs, a second period of the study begins in which the group that received the new drug now receives a placebo, and the group that received the placebo now receives the new drug. The crossover design allows for a better assessment of the effects of the drugs and the elimination of so-called "confounding" factors that can affect the effect of the drugs (e.g., patient habits).

4. phase: If the drug in phase 3 proves to be more effective than the existing treatment and is no longer toxic, it is approved for clinical use. From that moment on, phase 4 of clinical trials begins: long-term monitoring of the drug's side effects. Sometimes, it is only after many years that the drug is shown to be too toxic, and it is withdrawn from use..

SPECIAL PHARMACOLOGY

AUTONOMOUS NERVOUS SYSTEM

The nervous system can be divided into the central (brain and spinal cord) and the peripheral, which has two parts: somatic and autonomic. The somatic nervous system allows the control of voluntary movements, while the autonomic nervous system maintains the constancy of the internal environment, i.e. homeostasis. The autonomic nervous system has two parts: sympathetic and parasympathetic. Both parts control the functions of internal organs without the participation of consciousness, i.e., they regulate the work of the cardiovascular system, gastrointestinal tract, metabolism, body temperature and secretion of exocrine glands.

The sympathetic centers are located in the lateral horns of the spinal cord (from the 8th cervical to the 2nd lumbar segment). They are composed of so-called preganglionic neurons whose axons exit the spinal cord and reach the ganglia. The sympathetic ganglia form two chains with 22 ganglia each, located on the side of the spinal column. At the ends of these axons, the neurotransmitter acetylcholine is secreted. It binds to nicotinic receptors on the ganglion neurons and activates them. The ganglion neurons then send their axons to peripheral organs (heart, gastrointestinal tract, etc.). At the ends of these axons, the neurotransmitter noradrenaline is secreted, which binds to alpha or beta receptors on the membranes of cells of peripheral organs (smooth muscle cells, cells of exocrine glands, etc.). Binding to alpha or beta receptors results in the activation or inhibition of these cells (for example, smooth muscle cells contract or relax, cells of exocrine glands increase or decrease their secretion, etc.).

Activation of one preganglionic neuron of the sympathetic nervous system results in the activation of a larger number of ganglion cells, which ultimately leads to the activation of an even larger number of effector cells of peripheral organs. Activity initiated in sympathetic centers spreads exponentially through preganglionic and postganglionic fibers, activating multiple tissues and organs simultaneously.

Noradrenalin is synthesized in the endings of the postganging nervous fibers of the sympathetic nervous system, from the amino acid thyrosine. Tyrosine enters the nerve endings, and then in cytoplasm under the action of thyrosine hydroxylase turns into a dihydroxyphenylanine (DOPA). DOPA further under the influence of dopa-decarboxylase turns into dopamine. Dopamine then by active transport enters in synaptic vesicles, where under the action of dopamin-beta-hydroxylase turns to norepinephrine.

When the ganglionic cell of the sympathetic nervous system is activated, it sends action potential along its axon until its end. When the ending of the axon id depolarized, calcium from extracellular space enters the ending, and leads to exocytosis of vesicles with noradrenaline. Noradrenaline is released into a synaptic cleft, and acts on its receptors on the postsynaptic and presynaptic membranes.

The effect of noradrenaline stops after its uptake in the presynaptic ending (this process is called "uptake 1") or in the surrounding cells ("uptake 2"). Noradrenaline uotaken in the presynaptic ending is inactivated by monoamino-oxidase enzyme (MAO), and noradrenalin uptaken into the surrounding cells is inactivated by enzyme catechol-o-methyl transferase (COMT). MAO eliminates the amino group from amines, and introduces oxygen instead. COMT adds a methyl group to a hydroxyl group of catechol nucleus.

The part of the sympathetic system is also the medulla of the suprarenal gland, which conditionally we can understand as an altered sympathetic ganglia. The preganglionic fibers of the sympathicus after coming in the medula of the suprarenal gland release acetylcholine on their ends; Acetylholine then binds to nicotine receptors on medullar cells and activates them. Medular cells respond to the activation by secretion of adrenaline (epinephrine) in the bloodstream. Since the adrenaline is secreted directly into blood, we consider it to be a hormone, unlike noradrenaline, which is released from the sympathetic nerve endings into a synaptic cleft, and acts as a neurotransmitter.

Adrenaline is chemically different from noradrenaline only by one additional methyl group. Both compounds, like their precursor dopamine, have catechol in their molecule (benzol's ring with two OH-groups), so they are called a catecholamines.

Centers of parasympathicus are located in the nuclei of some cranial nerves (nervus occulomotorius, nervus facialis, nervus glossopharyngicus and nervus vagus) and in the side horns of the sacral part of the spinal cord (s2-s4 segments). Neurons from parasympathetic centers send their axons to the peripheral organs themselves (Figure 17). In the walls of peripheral organs (stomach, intestines, bronchi, urinary tract, etc.) ganglionic cells are situated, with which the axons of central neurons engage into synaptic contact. From the endings of these aksons, acetylcholine is released, which then activates nicotine receptors on ganglionic cells. Ganglionic cells have short axons ending on effector cells: myocardial cells, smooth muscle cells and cells of exocrine glands. The endings of the axons from ganglionic cell release neurotransmitter acetylcholine, which then binds to muscarine receptors on effector cells. The effects of acetylcholine on receptors are terminated relatively quickly, because it is broken down by the enzyme acetylcholinesterase, which is located next to the receptors.

Acetylholine is synthesized in cytoplasm of nerve endings, from choline and acetyl-coenzyme, under the catalytic action of choline acetyltransferase. The synthesized acetylcholine then enters the presynaptic vesicles with active transport, from where it is released after the depolarization of the nervous ending and calcium entry.

$CH_3 - COO - CH_2 - CH_2 - N^+ - (CH_3)_3$
Acetylcholine

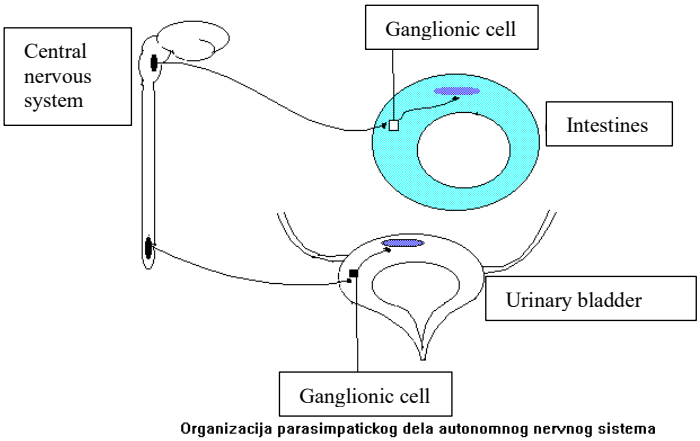


Figure 17. Parasympathetic nervous system.

Nicotinic receptors

Nicotinic receptors are located on the ganglionic cells of both sympathetic and parasympathetic nervous system. They belong to superfamily of receptors - ion channels. The receptors are named by nicotine, the alkaloid from tobacco, which binds to them and elicits activation. In physiological conditions, they are activated by acetylcholine, which is released from the endings of the preganglionic nerve fibers. The effect of acetylcholine binding is activation of the ganglionic cell and the further transmission of impulse to effector cells in peripheral organs. Nicotine receptors are also located on cells of the medulla of the suprarenal gland, where their stimulation leads to the release of adrenaline to bloodstream.

Location, function and types of alpha and beta receptors

Both alpha and beta receptors belong to a group of receptors related to G-proteins. There are two basic types of alpha receptors: Alfa1 and Alfa2. Alfa1 receptors are located on the membrane of smooth muscle arteries and veins in internal organs. Their activation by noradrenaline leads to an increase in the concentration of inositol three-phosphate and ion calcium within a smooth muscle cell, vasoconstration and rise in blood pressure. In addition, Alfa1 receptors are located in a sphincter of urinary bladder where their activation results with aggravated urination. Alfa2 receptors are located on the presynaptic endings of the nerve fibers from autonomous nervous system and their activation leads to the inhibition of adenilyl-cyclase enzyme and reduction of neurotransmitter release.

In some blood vessels (e.g., coronary arteries), in addition to Alpha1 receptors, there are Alfa2 receptors; they are partly localized on the membranes of endothelial cells (their activation leads to release of nitric oxide which further causes relaxation of smooth muscle cells in the arterial wall, i.e., vasodilation), and partly on smooth muscle cells, which are contracted when receptors are activated by noradrenaline, leading to vasoconstriction.

In the gastrointestinal tract, alpha1 receptors are on smooth muscle cells of sphincters; their activation leads to the contraction of the sphincters. Alfa2 receptors are present on ganglionic cells, where they reduce the release of acetylcholine, and thus inhibit peristaltic movements of intestines.

Less significant roles of alpha1 receptors are related to the contraction of m. dilatator pupillae (and consequently the dilation of the pupil), the increase in the force of contraction of the heart muscle, the acceleration of glucose metabolism, the contraction of the internal sphincter of the urinary bladder and the contraction of m. erector pili (the result is the upstanding of hairs).

There are three subtypes of alpha 1 receptors (A, B and D) and three subtypes of alpha2 receptors (A, B and C). Of the subtypes of alpha 2 receptors, only the B subtype can be found on the postsynaptic membrane.

Beta receptors exist in three forms: beta1, beta2 and beta3. All of these receptor types are associated with stimulation of the intracellular enzyme adenylyl cyclase, which generates cAMP from ATP. Beta1 receptors are found in the heart and on the cells of the juxtaglomerular apparatus of the kidney; their activation leads to an acceleration of the heart rate, an increase in the force of contraction, an increase in the speed of conduction and an increase in the excitability of the heart cells. Activation of beta1 receptors in the kidney leads to an increase in the secretion of renin, which results in an increase in blood pressure. Beta2 receptors are found on the smooth muscle cells of the bronchi, where they lead to relaxation and bronchodilation. In addition, they are found on the muscles of the uterus, the bladder (they relax them) and in the blood vessels that nourish the extremities (they lead to vasodilation). Beta3 receptors are found on adipose tissue cells; their activation is accompanied by an increase in the intensity of lipolysis.

Beta2 receptors are also found on striated muscle cells, where they increase the entry of potassium ions into the sarcoplasm. On liver cells, beta2 receptors activate the process of glycogenolysis, which results in an increase in glycemia. Also, a smaller number of beta2 receptors are found in the myocardium, where, like beta1 receptors, they increase the force of contraction.

Insulin secretion from endocrine cells of the pancreas is stimulated by beta receptors and inhibited by alpha2 receptors.

Receptors of parasympathetic nervous system

On the effector cells of peripheral organs (heart, gastrointestinal tract, bronchi, bladder, etc.) there are muscarinic receptors that are activated by acetylcholine. Muscarinic receptors belong to the group of G-protein-coupled receptors. They were named after the alkaloid of the Amanita muscaria mushroom, muscarine, which activates them. There are 5 types of muscarinic receptors (M1, M2, M3, M4, M5). Stimulation of M1, M3 and M5 receptors increases the concentration of inositol triphosphate and diacylglycerol in the cytoplasm (which leads to an increase in the concentration of calcium in the cytoplasm), and activates adenylate cyclase, while stimulation of M2 and M4 receptors inhibits the activity of adenylate cyclase (stimulation of M2 receptors additionally opens potassium ion channels). M1 receptors are found in the brain, on autonomic ganglia, on parietal cells in the gastric mucosa, and on smooth muscle cells of the gastrointestinal tract. Their stimulation by acetylcholine leads to increased secretion of hydrochloric acid and contraction of smooth muscles. M2 receptors are found primarily in the heart, where their stimulation leads to a slowdown in heart rate, a decrease in the force of cardiac contraction, a slowdown in conduction, and a decrease in the excitability of cardiac cells. In addition to the heart, M2 receptors are found in the brain and autonomic ganglia. M3 receptors are found on smooth muscle cells of the respiratory, gastrointestinal, and genitourinary tracts; their stimulation leads to contraction. In addition to smooth muscle cells, M3 receptors are found on exocrine glands, in the brain, and on endothelial cells. M4 receptors are present in the brain and on autonomic ganglia, while M5 receptors are only in the brain.

Clinically significant drugs that act via the sympathetic nervous system

Drugs that mimic the effects of sympathetic nervous system activation are called sympathomimetics. They can act directly on alpha and beta receptors, when they are called direct sympathomimetics, or they can cause the release of noradrenaline from sympathetic nerve endings (indirect sympathomimetics). Indirect sympathomimetics either directly release noradrenaline from synaptic endings or inhibit its removal from the synaptic cleft. Amphetamine causes the release of noradrenaline from nerve endings, and because of this action it causes tachycardia and hypertension. Since it penetrates the blood-brain barrier and enters into the CNS, it also has central stimulant effects: euphoria, loss of appetite, increased alertness, and in toxic doses convulsions. Ephedrine also acts similarly to amphetamine; only its effect is much longer because it is metabolized more slowly.

Ephedrine is known to lose its effect after one day of use, i.e., the noradrenaline depots are emptied from the nerve endings. This type of tolerance, which occurs quickly (within 1 day), is called tachyphylaxis.

Cocaine blocks the process of noradrenaline uptake into the presynaptic terminal ("uptake 1") and thus leads to the accumulation of noradrenaline near the receptors. In addition, it blocks Na+ channels in the neuronal membrane and thus prevents the transmission of impulses along the axon. Due to these effects, it has been used as a surface local anesthetic in otorhinolaryngology and ophthalmology: it successfully anesthetizes the mucous membrane and leads to its decongestion due to its vasoconstrictor effect.

Indirect sympathomimetics include sibutramine, a drug that inhibits the reuptake of noradrenaline and serotonin. Since it penetrates the central nervous system, this drug is used to suppress appetite and treat obesity.

Agonists of alpha and beta receptors are direct sympathomimetics. According to their chemical structure, they can be classified as catecholamines (which have a catechol ring: a benzene ring with two hydroxy groups in the meta position) and non-catecholamines. Adrenaline (epinephrine) is a natural substance that is produced in the adrenal medulla by methylation of noradrenaline. It belongs to the catecholamines. It activates both alpha and beta receptors, but the effect on beta receptors is more pronounced. It leads to stimulation of the heart (increased force of contraction, increased heart rate, increased conduction velocity in the heart and increased irritability), vasodilation in skeletal muscles (beta2-effect) and vasoconstriction in the skin and internal organs (alpha1-effect). As a result of these effects, tachycardia and an increase in systolic blood pressure occur. Due to the aforementioned effects, adrenaline is used in the treatment of anaphylactic shock and cardiac arrest (since it is broken down in the digestive tract, it is administered only parenterally - 0.3 mg intramuscularly or 0.2 mg intravenously, diluted with saline in a ratio of 1:10). Since adrenaline has a bronchodilator effect by activating the beta2-receptor, it can be used to treat asthma attacks. Adrenaline is added in small amounts to local anesthetic solutions to slow their resorption from the site of application and thus prolong their effect.

When administering adrenaline, it should be known that it is metabolized extremely quickly, so the effect of the administered dose quickly passes; a new dose should be given after 10-20 minutes!

Alpha-receptor agonists are also direct sympathomimetics. Of the natural substances, the catecholamine noradrenaline has the greatest affinity for Alpha-receptors. However, it is not entirely selective: it also activates beta-receptors to a lesser extent. Noradrenaline increases the force of myocardial contraction (with an increase in oxygen consumption) by directly acting on the heart, and increases both systolic and diastolic arterial blood pressure by acting on alpha1 receptors on smooth muscle cells of blood vessels (which leads to vasoconstriction and an increase in peripheral resistance to blood flow). Due to the jump in blood pressure, baroreceptors are activated, so parasympathetic fibers for the heart are reflexively activated, causing a slow heart rate, i.e. bradycardia.

There are many synthetic substances that selectively activate alpha-receptors: phenylephrine, naphazoline, xylometazoline, methoxamine, metaraminol, etc. Of the alpha-agonists used in practice, only noradrenaline is used (as an intravenous infusion, to suppress hypotension during spinal anesthesia or other conditions where peripheral resistance to blood flow is low; it is rarely used in shock therapy, because at that time the sympathetic nervous system is already maximally activated, so additional amounts of adrenaline would only worsen the perfusion of vital organs), and phenylephrine, xylometazoline and naphazoline (in the form of nose drops, because they lead to vasoconstriction and decongestion of the nasal mucosa). Phenylephrine is also used in ophthalmology, to cause mydriasis; However, it should be noted that its use in angle-closure glaucoma (acute glaucoma) is contraindicated, as it may further complicate the outflow of aqueous humor, thereby increasing intraocular pressure. The main reason for the use of alpha-agonists is their vasoconstrictor effect. The main danger in their use lies in the possibility of overdose, which leads to a dangerous increase in blood pressure and bleeding in the brain. In addition, noradrenaline can cause arrhythmias due to stimulation of beta-receptors in the heart.

Although phenylephrine, naphazoline and xylometazoline very effectively cause vasoconstriction and decongestion of the nasal mucosa, after their effect ceases, reactive hyperemia of the nasal mucosa occurs and even greater congestion occurs than before the use of these drugs in the form of nasal drops. This forces the patient to reach for the drops again, and the conditions are created for the formation of a vicious circle, i.e. "circulus vitiosus". Patients should be warned to use nasal drops as short as possible and in the lowest possible dose.

While the effect of noradrenaline and adrenaline lasts for a short time, because they are quickly broken down by MAO and COMT, the effects of metaraminol and methoxamine last much longer, and over 1 hour, because they are not subject to the catalytic action of these two enzymes.

Alpha-receptor blockers. Alpha-receptor blockers can block both alpha1 and alpha2 receptors (phentolamine, phenoxybenzamine) or only alpha1 (prazosin, terazosin, doxazosin, tamsulosin, urapidil) or alpha2 receptors (yohimbine). The alpha2 selective blocker yohimbine is not used in medical practice, but is abused due to its stimulating effects on the central nervous system (irritability, increased motor activity, tremor) because it is mistakenly believed to have an aphrodisiac effect. Phentolamine and phenoxybenzamine are used only for the treatment and preoperative preparation of patients with pheochromocytoma (adrenal medulla tumor). The blood of patients with this tumor contains a high concentration of adrenaline and noradrenaline, which is why the patient has extremely high blood pressure, which can lead to bleeding in the brain. Intravenous administration of phentolamine can quickly (but briefly) control blood pressure and reduce it to normal values. This is used during surgical intervention to remove a tumor (1 hour before surgery, 10 mg of phentolamine is administered intravenously). Over a longer period of time, while preparing for surgery, the patient can take phenoxybenzamine orally (the initial dose is 10 mg/12 hours, gradually increasing to 1-2 mg/kg/day). It has a long-lasting effect (over 24 hours) because it irreversibly blocks alpha-

receptors. Phentolamine and phenoxybenzamine are not used to treat essential hypertension because they have a significant side effect - reflex tachycardia. Both drugs lead to a significant drop in blood pressure (orthostatic or postural hypotension), which activates baroreceptors in the aortic arch and carotid sinus and reflexively causes an acceleration of the heart rate. This difficulty is partially overcome by the alpha1-selective blockers prazosin and terazosin. Prazosin does not block presynaptic alpha2 receptors, so the high level of released noradrenaline due to the blockade of postsynaptic alpha1 receptors freely activates alpha2 receptors and inhibits further release of noradrenaline. As a result, reflex tachycardia is much less pronounced than with nonselective alpha-blockers.

In addition to selective blockade of alpha1 receptors, in higher doses prazosin has a direct vasodilating effect: in vascular smooth muscle cells it inhibits phosphodiesterase, increases the level of cyclic nucleotides and relaxes the cells. Prazosin is successfully used for the treatment of essential hypertension, but also for the treatment of Raynaud's disease (hyperactivity of the sympathetic nervous system resulting in vasoconstriction in the fingers).

Since the blockade of alpha1-receptors in the muscular capsule of the prostate leads to relaxation, prazosin facilitates urination in patients with prostatic hypertrophy. Both prazosin and other selective alpha1-blockers can be used for the symptomatic treatment of obstruction in prostatic hypertrophy; by blocking alpha1 receptors in the internal urethral sphincter they facilitate urination. Tamsulosin is particularly useful for this indication, as it selectively blocks alpha1A receptors (which dominate the internal urethral sphincter), while its effect on alpha1B receptors, which dominate the smooth muscle cells of blood vessels, is significantly lower.

The dose of prazosin for the treatment of hypertension is usually 1 mg/8 hours orally, but it can be increased to 20 mg/day if a satisfactory effect is not achieved with lower doses. It is very important to know that after the first dose of prazosin, an extremely large drop in blood pressure can occur; to avoid this, the patient should take the first dose of prazosin just before going to bed.

Prazosin can also cause postural hypotension as a side effect (the phenomenon that blood pressure decreases further when taking an upright position, so that due to reduced cerebral perfusion the patient feels dizzy and unsteady; rarely, loss of consciousness can occur), but it occurs much less frequently and in a milder form than with the use of phenoxybenzamine or phentolamine. Postural hypotension occurs much more often if the patient has a sodium deficiency (e.g., with dehydration, long-term use of diuretics or a long-term salt-free diet).

Urapidil is an alpha 1 blocker for parenteral administration, which is used in the treatment of hypertensive crisis. In addition to blocking alpha 1 receptors, urapidil also acts by a central mechanism, because it reduces sympathetic activity.

Beta receptor agonists. Beta-receptor agonists can be non-selective (they activate both beta1, beta2 and beta3 receptors: isoprenaline and orciprenaline), they can activate only beta1 (dobutamine) or only beta2 receptors (salbutamol, fenoterol, hexoprenaline, ritodrine). Non-selective beta-agonists were once widely used to treat asthma attacks because by stimulating beta2 receptors on bronchial smooth muscle, they lead to bronchodilation. However, due to their non-selectivity, they also activate beta1 receptors located in the heart, leading to its stimulation (acceleration of the heart rate, increase in the force of cardiac contraction, acceleration of conduction and increased excitability of heart cells). Stimulation of the heart requires higher oxygen consumption in the myocardium, which must be met by increased blood flow through the coronary arteries. If the patient has narrowed coronary arteries due to atherosclerosis, ischemia and even myocardial necrosis may occur after the administration of isoprenaline or orciprenaline. Because of this side effect, non-selective beta-agonists are now rarely used for this indication; their place in the treatment of asthma has been taken by selective beta2 agonists, in which cardiac stimulation is much less pronounced (but it is still there!). Salbutamol and fenoterol can be administered by inhalation (aerosol) or orally. Two other beta2 selective agonists, ritodrine and hexoprenaline, have also found wide application in practice. They have a special affinity for beta2 receptors located in the myometrium. By stimulating these receptors, they cause relaxation of the uterus, especially in pregnancy (tocolytic effect). Such an effect is of great importance for the prevention and suppression of premature uterine contractions during pregnancy; ritodrine or hexoprenaline can stop a threatened miscarriage and delay premature birth. They are administered orally or intravenously. The oral dose of ritodrine is 10 mg / 4-6 hours, and intravenously 0.15-0.3 mg/min, until uterine contractions cease. Today, it is considered that there is no point in administering tocolytics for more than 72 hours; if uterine contractions do not cease within that time, further administration of tocolytics is also ineffective. The only thing that patients get when administering tocolytics for more than 72 hours is unpleasant side effects: palpitations and tremors.

In addition to unwanted cardiac stimulation, all β-agonists cause tremor at rest (which can sometimes interfere with normal activities), nervousness, dizziness, and nausea.

Dobutamine, as a selective beta1-receptor agonist, is currently used to treat cardiogenic shock. Its advantage over dopamine is that it increases myocardial oxygen consumption less, so there is less chance of myocardial hypoxemia due to strong cardiac stimulation. Unlike dopamine, dobutamine **does not dilate renal and mesenteric blood vessels**. However, dobutamine is not

absolutely selective: it activates beta 2 and alpha 1 receptors to a small extent. The half-life of dobutamine is only 2 minutes, because it is very rapidly degraded by catechol-o-methyltransferase in the liver.

β-receptor blockers. Beta-blockers competitively block beta-receptors, preventing the action of natural transmitters, noradrenaline and adrenaline. Some beta-blockers also have some intrinsic activity at beta-receptors, i.e., they act as partial agonists. In addition, beta-blockers reduce the excitability of the cell membrane, i.e. they act as membrane stabilizers, similar to local anesthetics.

Non-selective β-blockers (propranolol, pindolol) reduce heart rate (reduce the force of contraction, reduce the frequency, conduction velocity and excitability), have an antiarrhythmic effect and lead to a decrease in blood pressure. The hypotensive effect is also contributed by the reduced production of renin in the juxtaglomerular cells of the kidneys, which are normally controlled by β1-receptors. The hypotensive effect is not manifested immediately after administration of the drug (acutely), because peripheral resistance to blood flow increases reflexively. However, peripheral resistance gradually decreases, so the effect of **chronic** administration of these drugs is a decrease in blood pressure. In addition to being used as antiarrhythmics and antihypertensives, these drugs are also used in the treatment of angina pectoris; although beta-blockers reduce blood flow through the coronary arteries (which could have a detrimental effect in angina pectoris), they reduce the total work of the heart and thus oxygen consumption in the myocardium much more, which has a positive effect. Clinical studies have shown that the use of beta-blockers after myocardial infarction significantly reduces the risk of re-infarction.

Beta-blockers are used for the long-term treatment of patients with mild to moderate **heart failure**. In this condition, the sympathetic nervous system is overactive, trying in an inappropriate way to increase perfusion of vital organs (brain, kidneys, and liver). The myocardium then consumes more oxygen, because it must pump blood at a higher frequency, against increased peripheral resistance. The use of beta-blockers reduces excessive stimulation of the myocardium, lowers blood pressure, and allows better perfusion of organs and tissues with the same energy expenditure.

It is very useful to use beta-blockers in patients with hyperthyroidism, because they reduce the exhausting hyperactivation of the heart and tremor. They are especially useful in the treatment of thyrotoxic crisis, in preparing patients for thyroidectomy, as well as in the initial period of administering antithyroid drugs.

In addition to all of the above, beta-blockers have several other indications for use. Since they reduce the production of aqueous humor in the ciliary body, beta-blockers are successfully used in glaucoma, especially **chronic glaucoma**. **Timolol and betaxolol** are used for this indication, in the form of eye drops. Beta-blockers can also suppress peripheral manifestations of anxiety (palpitations, tremors) and may be useful in preventing **migraine** attacks..

The side effects of these drugs are an extension of their basic pharmacological action. Since they slow down the conduction of impulses in the heart, they can lead to A-V block, so their simultaneous use with other drugs that depress conduction in the heart (e.g. calcium channel blockers) should be avoided. Due to the blockade of beta2-receptors in the blood vessels of the extremities (which otherwise cause vasodilation after stimulation), ischemic disease may worsen, and due to the blockade of beta2-receptors on liver cells, the release of glucose from hepatocytes under the influence of adrenaline is prevented. Since glycogenolysis in the liver is important for the correction of hypoglycemia, especially in patients with diabetes receiving insulin, beta-blockers should be used very cautiously in diabetics, otherwise they can **worsen hypoglycemia** and increase its detrimental effect on the central nervous system. On the other hand, beta-blockers also reduce insulin secretion from pancreatic beta cells and interfere with the entry of glucose into muscle cells. The overall result of the effect of beta-blockers on glucose metabolism is a tendency towards hyperglycemia and the development or worsening of diabetes.

In addition to the above, in people with severe but still compensated heart failure, blockade of beta-receptors in the heart can lead to decompensation due to a negative inotropic effect. These drugs are contraindicated in patients with bronchial asthma, because blockade of beta2-receptors in the bronchi can lead **to bronchospasm**.

Those beta-blockers that are more liposoluble, and therefore better penetrate the central nervous system, can cause **nightmares**, depression, insomnia and hallucinations. The use of beta-blockers in men also creates an additional problem: the occurrence **of impotence**.

In an attempt to avoid these side effects, drugs **that selectively block only** β1-receptors have been synthesized: atenolol, carvedilol, bisoprolol, metoprolol, etc. However, their selectivity is not absolute - and they (although less frequently) can cause the same side effects. Another attempt to avoid side effects was the synthesis of β-blockers that are partial agonists, i.e., in addition to blocking the action of endogenous catecholamines on β-receptors, they also activate these receptors to a certain extent. However, the clinical use of these drugs (pindolol, alprenolol) has not confirmed this assumption, so their advantage over classical beta-blockers has not been proven. Propranolol is metabolized in the liver rapidly, already during the first pass. That is why its oral dose is 10 times higher than the intravenous dose! It is highly liposoluble, so it penetrates the CNS and sometimes causes unwanted central effects (nightmares, depression, confusion). Metoprolol, a selective beta1-blocker, behaves similarly. Bisoprolol is the

most widely used selective beta1-blocker in practice today, because it practically does not penetrate the central nervous system and has a so-called balanced elimination, i.e., it is both metabolized by the liver and excreted largely unchanged in the urine. In case of renal or hepatic insufficiency, it is not necessary to adjust the dose of bisoprolol.

Acebutolol, a selective beta1-blocker with partial agonist activity, has a bioavailability of about 50% after oral administration. It is metabolized in the liver to the active metabolite.

A very special beta-blocker is **esmolol**, selective for beta1-receptors, which is extremely rapidly degraded: the half-life is only 9 minutes. Esmolol is degraded by esterases in red blood cells. Due to its short duration of action, esmolol is used intravenously to control ventricular arrhythmias in emergency situations.

Drugs that block both alpha and beta receptors. The prototype of this group of drugs is labetalol, which blocks beta and alpha receptors in a ratio of 3-7:1. Its beta-blocking effect is 3 times weaker than propranolol, and its alpha-blocking effect is 10 times weaker than that of phentolamine. Labetalol is also a partial agonist of beta receptors, and it also has a stabilizing effect on membranes. In addition to all the effects mentioned, labetalol can block the reuptake of noradrenaline and dopamine into nerve endings, which is why it sometimes paradoxically causes a jump in blood pressure upon first administration.

After absorption from the intestine, labetalol undergoes first-pass metabolism in the liver and is transformed into inactive glucuronide conjugates.

Labetalol reduces peripheral resistance to blood flow and lowers blood pressure, with a minimal decrease in heart rate, significantly less than after the use of other beta-blockers. It is used for the treatment of hypertension orally, but also for the treatment of **hypertensive crisis** intravenously.

In addition to postural hypotension, inability to ejaculate, fatigue, exacerbation of bronchial asthma and exacerbation of severe heart failure, labetalol can cause the appearance of anti-nuclear antibodies in a small number of patients, and very rarely a condition similar to **systemic lupus erythematosus**.

In terms of effects, **carvedilol** is very similar to labetalol, a drug with combined alpha and beta blocking effects, which is widely used today for the treatment of chronic, mild to moderate, heart failure.

A drug that reduces the synthesis of catecholamines. Metyrosine is a drug that inhibits tyrosine hydroxylase, an enzyme that converts tyrosine to DOPA. It is used for preoperative preparation as well as for the treatment of patients with pheochromocytoma (if they cannot undergo surgery for any reason).

Ergot alkaloids

The fungus **Ergot (Secale cornutum)**, which parasitizes rye and other cereals, synthesizes a large number of pharmacologically active substances that belong to the group of alkaloids (i.e., exhibit a basic reaction). Although some authors classify Ergot alkaloids as alpha blockers, their action is complex and is a consequence of binding to at least three types of receptors: alpha-adrenergic, dopamine receptors, and serotonin (5-hydroxytryptamine) receptors. Of these alkaloids, ergotamine and ergometrine are of clinical importance. **Ergotamine** causes strong vasoconstriction of the arteries of the extremities and closes the arteriovenous communications in the neck; both effects result in better blood circulation and oxygenation of the head. Therefore, ergotamine is successfully used to stop migraine attacks (one 2 mg lingual tablet should be placed under the tongue as early as possible after the onset of the attack). **Ergometrine and its semi-synthetic derivative methyl-ergometrine** (dose 0.2 mg intramuscularly) in addition to their vasoconstrictor effect have a strong spasmogenic effect on the uterus: they cause prolonged, tonic contraction of the uterus, thereby reducing blood flow through this organ. They are used to stop bleeding in the fourth stage of labor, after the birth of the fetus and the elimination of the placenta. It should be remembered that they should never be given before the birth of the fetus because they can lead to interruption of blood flow through the placenta and/or rupture of the uterus!

The main problem with the use of these drugs is vasoconstriction in the extremities and an increase in blood pressure. In the Middle Ages, poisoning with bread made from rye with a lot of ergot was very widespread. In those poisoned, due to intense vasoconstriction, necrosis of the distal parts of the extremities occurred, which would turn black and look as if they had been burned (hence the name "St. Anthony's fire"). Since ergot alkaloids also include lysergic acid diethylamide (LSD), the poisoned had hallucinations and fell into delirium. It is believed that the strange behavior of the "witches" who were later burned can be attributed to poisoning by ergot alkaloids!

If two hydrogens are added to ergot alkaloids, dihydrogenated derivatives are obtained that behave differently; some of them acquire an alpha-blocking effect, thus leading to vasodilation! Dihydroergotoxine is such a derivative of ergotoxine; It is used to treat hypertension and senile dementia due to arteriosclerosis (however, its efficacy is very low, so it will most likely soon be withdrawn from clinical practice, i.e. declared as an obsolete drug).

Dopamin

Dopamine is a catecholamine that functions as a neurotransmitter in both the central nervous system and the periphery. Outside the central nervous system, dopamine in lower concentrations acts only on its specific dopamine receptors in the arteries of the kidneys, myocardium, brain, and mesentery, causing vasodilation. Activation of D1 dopamine receptors (found on blood vessels) leads to vasodilation, increased diuresis, and increased sodium excretion. Activation of D2 dopamine receptors (found on ganglion cells, adrenal cortex, sympathetic nerve endings, and in the cardiovascular center in the medulla oblongata) leads to bradycardia, hypotension, and vasodilation in the kidney.

At higher concentrations, dopamine increases the release of noradrenaline, and stimulates beta1 receptors in the heart (causing an increase in heart rate, increased contraction, faster conduction, and increased excitability). Systolic blood pressure then rises, while diastolic pressure remains the same.

At very high concentrations, dopamine also activates alpha1 receptors in blood vessels (causing vasoconstriction). Both systolic and diastolic blood pressure increase.

When administered carefully (in lower doses, 5-10 mcg/kg/min), dopamine is extremely useful in treating shock because it stimulates the heart and maintains blood flow through the kidneys, preventing the development of acute renal failure.

Clinically significant drugs that act via the parasympathetic system

Nicotine. Nicotine is an alkaloid found in tobacco leaves. It binds to nicotinic receptors, which it first activates and then blocks (because it leads to permanent depolarization of the cell, which can no longer respond to new stimuli). The effect of nicotine, which is introduced into the body through smoking, represents a combination of the effects of activation of the autonomic ganglia and central effects. Due to the activation of the sympathetic ganglia, the heart rate accelerates and blood pressure rises. Due to the activation of the parasympathetic ganglia, the secretion of exocrine glands increases and the motility of the digestive tract accelerates.

By acting on the central nervous system, it improves memory, reduces aggression, reduces appetite and increases the release of antidiuretic hormone. Such pleasant central effects are the main reason for enjoying tobacco. In people who are not accustomed to tobacco, nicotine can cause vomiting by directly stimulating the vomiting center in the brainstem. In larger doses, nicotine can cause tremors and convulsions.

Small doses of nicotine stimulate breathing by activating chemoreceptors in special bodies, which are located near the aortic arch and carotid sinus. In larger doses, nicotine also stimulates breathing, but by directly acting on the respiratory center.

Nicotine is otherwise one of the most toxic substances. The lethal dose is only 50-60 mg. The patient dies due to paralysis of the respiratory muscles (partly due to depression of the respiratory center, and partly due to blockade of neuromuscular transmission).

Nicotine is a lipophilic substance, which is easily absorbed from the site of application, and penetrates the blood-brain and placental barriers (98% of nicotine is absorbed from inhaled tobacco smoke!). It is metabolized in the liver, kidneys and lungs; nicotine metabolites are excreted in the urine.

Direct muscarinic receptor agonists (direct cholinomimetics). These can be natural substances (e.g. pilocarpine) and synthetic choline esters: methanechol, bethanechol and carbachol. All of these substances act on muscarinic receptors like acetylcholine, but are more resistant to the action of acetylcholinesterase; they can be used clinically because their effect lasts long enough (the action of acetylcholine lasts only a few minutes). While pilocarpine, methacholine and bethanechol are selective agonists of muscarinic receptors, carbachol activates both nicotinic and muscarinic receptors.

Synthetic choline esters are, like acetylcholine, quaternary nitrogen compounds, which means that they do not penetrate the blood-brain barrier. Pilocarpine, on the contrary, is a tertiary amine.

After systemic administration in small doses, choline esters cause vasodilation, a drop in blood pressure and reflex tachycardia (due to activation of baroreceptors). At higher doses, their direct effect on M2 receptors in the SA and AV nodes dominates, resulting in bradycardia and slowing of impulse conduction in the AV node. Due to the stimulation of muscarinic receptors in other organs, these substances cause, among other things: increased salivation and acid secretion, increased intestinal peristalsis, bronchoconstriction and facilitated urination.

Bethanechol is sometimes used to stimulate intestinal peristalsis in patients with paralytic ileus, and to prevent urinary retention after pelvic surgery. Methacholine is of diagnostic value only: its administration by inhalation can detect patients with asthma, as it causes excessive bronchoconstriction (methacholine test). Pilocarpine is used in ophthalmology to treat acute

glaucoma. After topical application to the conjunctiva, pilocarpine is absorbed and causes contraction of the ciliary muscle and pupillary sphincter.

Inhibitors of acetylcholinesterase. Blockade of the acetylcholinesterase enzyme prevents the breakdown of acetylcholine and it accumulates in the synaptic cleft, near its receptors. This allows the receptors to be stimulated for longer and more strongly, resulting in clinically significant effects. In healthy individuals, these are reflected in signs of stimulation of the parasympathetic nervous system (acceleration of peristalsis in the digestive tract, increased secretion of exocrine glands, bronchoconstriction, miosis, accommodation spasm, sweating) and the central nervous system, but only on condition that the cholinesterase blocker passes through the blood-brain barrier (in therapeutic doses, a slight increase in alertness, and in toxic doses, convulsions, then coma and paralysis of the respiratory center occur). Fasciculations are initially seen in the muscles, followed by paralysis, due to desensitization of nicotinic receptors under the constant action of acetylcholine (desensitization: activation of the receptor no longer produces the same effect in the cell).

Acetylcholinesterase inhibitors are more selective in their action than direct cholinomimetics, as they activate muscarinic and nicotinic receptors only at active cholinergic synapses. They also do not stimulate muscarinic receptors on endothelial cells, as there are no synapses there.

Acetylcholinesterase inhibitors can be classified into four groups, which differ in the way they inhibit the enzyme and their clinical significance. **Quaternary ammonium compounds (edrophonium and ambenonium**) bind to the anionic site on the enzyme, to which acetylcholine normally binds, and thus competitively prevent the breakdown of acetylcholine. The action of edrophonium lasts only 5-10 minutes, and that of ambenonium for as long as 4-8 hours. Both of these drugs also have some direct agonistic effect on nicotinic receptors. **Carbamates (carbamic acid esters: neostigmine, physostigmine, pyridostigmine, rivastigmine)** carbamylate the esterase site on the acetylcholinesterase enzyme and inactivate it; the carbamino radical then slowly spontaneously hydrolyzes from the esterase site, so that the enzyme becomes active again. **Organophosphates (insecticides parathion and malathion, isofluorophore, echothiophate, nerve agents sarin, soman, tabun and ve-ix**) irreversibly inactivate the esterase site of acetylcholinesterase by covalently binding to that site. **Central nervous system** acetylcholinesterase inhibitors (tacrine, donepezil, the zelentide alkaloid galantamine) are chemically diverse compounds that somewhat specifically and reversibly inhibit acetylcholinesterase in the CNS.

Quaternary ammonium compounds (edrophonium, ambenonium, but also neostigmine and pyridostigmine) do not penetrate the blood-brain barrier, but are sufficiently well absorbed from the digestive tract; therefore, neostigmine and pyridostigmine can also be administered orally. Other acetylcholinesterase inhibitors are well absorbed from the digestive tract, and penetrate well into the central nervous system (CNS). Organophosphates are very liposoluble, so they can be absorbed through the skin to a high extent. Both carbamates and organophosphates are broken down by hydrolysis in the blood and many organs, and their metabolites are excreted in the urine.

Due to their effect on peristalsis, some of these drugs (neostigmine, e.g.) are used to treat paralytic ileus. These drugs have much greater therapeutic importance in situations where neuromuscular transmission is impaired, which is also carried out with the help of acetylcholine as a mediator. Neostigmine is successfully used in myasthenia gravis, a disease in which the number of nicotinic receptors in the neuromuscular synapse is reduced. By blocking cholinesterase, neostigmine leads to the accumulation of acetylcholine, which now activates the remaining nicotinic receptors more effectively. In addition to neostigmine, pyridostigmine is also used for the same indication, whose effect lasts longer. In addition, neostigmine is used when it is desired to interrupt the neuromuscular blockade caused by nicotinic receptor blockers (muscle relaxants) during anesthesia.

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Physostigmine can also be used as an antidote in acute poisoning with anticholinergic drugs (atropine, scopolamine, etc.). However, due to the possibility that it itself can cause cardiac arrhythmias or convulsions, it is used only in situations where the

patient's life is at risk. It is especially important not to use it in poisoning with antidepressants with anticholinergic effects, because then it almost certainly causes convulsions in the patient. Cholinesterase blockers are widely used as insecticides and, unfortunately, as weapons. These are compounds from the carbamate group (e.g. carbaryl) that reversibly block acetylcholinesterase and compounds from the organophosphate group (i**nsecticides: parathion, malathion; weapons: sarin, soman, tabun, ve-ix**) that block this enzyme irreversibly. Due to their widespread use, poisonings with these substances are common, causing signs of excessive parasympathetic stimulation, convulsions, coma, respiratory paralysis and neuromuscular paralysis due to prolonged stimulation and desensitization of nicotinic receptors. Poisoning is treated with **atropine** (in single doses of 1 mg, until clinical signs of excessive stimulation of parasympathetic nerves disappear) which blocks muscarinic effects and **oximes (e.g. pralidoxime)** which unblocks acetylcholinesterase and enables it to function normally. Oximes are all the more effective if they are administered earlier, because over time the covalent bond of the poison with the enzyme "ages", and the drug is no longer able to break it.

Since pralidoxime is a quaternary ammonium compound, it does not penetrate the CNS and cannot unblock acetylcholinesterase in central synapses. The dose of pralidoxime is 1-2g, intramuscularly or intravenously. Oximes are only effective in organophosphate poisoning; in carbamate poisoning, the effect is zero.

When people poisoned by organophosphates receive treatment (atropine and pralidoxime), their condition improves quickly, but they must remain hospitalized for the next few days. The reason for this is the possibility of redistribution of the poison, which moves from the fatty tissue into the blood, and then into the brain and muscle tissue, where it again causes toxic effects a day or two after the poisoning. This phenomenon is called "**delayed toxicity syndrome**", and it should always be considered when treating people poisoned by organophosphates.

Some organophosphates (weapons) can cause neuropathy, with muscle weakness, which gradually progresses to flaccid or spastic paralysis, months or years after entering the human body. This effect was observed in American veterans of the "Gulf War" between the USA and Iraq. The reason for the development of polyneuropathy is the blockade of the **neurotoxic esterase** enzyme in muscle tissue.

Muscarinic receptor blockers. Alkaloids from nightshade and valerian, **atropine and scopolamine**, competitively block muscarinic receptors and cause effects opposite to parasympathetic activation: tachycardia, relaxation of the gastrointestinal muscles, difficulty urinating, mydriasis and paralysis of accommodation, bronchodilation, decreased secretion of salivary and bronchial glands. In addition, they penetrate the CNS and cause first amnesia, impaired concentration and drowsiness, and later confusion, ataxia, asynergia, delirium and very rarely coma (the set of these symptoms is called "**central anticholinergic syndrome**"). Due to the blockade of muscarinic receptors in the vestibular nuclei and the vomiting center, they prevent vomiting while driving (motion sickness) if taken before setting off on a journey. Anticholinergic drugs do not affect blood vessels significantly (except for mild flushing of the face and upper chest), because the muscarinic receptors on endothelial cells are not part of the cholinergic synapse, but are located there independently.

Sometimes atropine or scopolamine in small doses can **cause paradoxical bradycardia**. The reason for this is the blockade of very sensitive presynaptic muscarinic receptors, which normally inhibit the release of acetylcholine.

Atropine is a tertiary amine, but also a **racemate**, a mixture of D- and L-hyoscyamine. Atropine is used in the treatment of bradycardia or cardiac arrest due to excessive parasympathetic activation /during endoscopy, induction of anesthesia/ and in premedication for general anesthesia because it reduces secretion in the bronchial tree. Atropine can also be used to diagnose SA node dysfunction in the heart: if sinus bradycardia is due to extracardiac causes, atropine will speed up the heart rate, and if the problem is in the SA node itself, there will be no change. People with syncope due to carotid sinus hypersensitivity can also benefit from taking atropine, which prevents extreme reflex bradycardia. **Scopolamine** is applied transdermally, using a patch from which it is absorbed through the skin (due to its high liposolubility); prevents vomiting due to driving, but only if the patch is applied before setting off.

Atropine and scopolamine are well absorbed, and easily penetrate the CNS. The inactive isomer of atropine, D-hyoscyamine, is excreted unchanged in the urine, while the active isomer, L-hyoscyamine, is first oxidized and hydrolyzed.

A large number of semi-synthetic and synthetic substances have been found that block muscarinic receptors, such as scopolamine and atropine. Some of them penetrate well into the CNS and are used in situations where a decrease in the activity of cholinergic pathways is desirable. One such drug is **trihexyphenidyl**, which is used in the treatment of Parkinson's disease (in this disease, the dopaminergic nigrostriatal pathways that normally keep the balance with the cholinergic striatonigral pathways are damaged; the latter become excessively active). The second group consists of highly polar compounds (**quaternary ammonium** bases: 4 functional groups are attached to nitrogen) that do not enter the CNS and are widely used in the treatment of spasms of the smooth muscles of the ureter (renal colic), intestines (intestinal colic) and biliary tract (biliary colic). Such drugs are **scopolamine-butylbromide and propantheline**.

A special group of anticholinergic drugs consists of **oxybutynin, dicyclomine and tolterodine**, which are used to reduce bladder reactivity, i.e. in the condition of uninhibited bladder, bladder spasm, nocturia and incontinence. Tolterodine acts to a certain extent selectively on muscarinic receptors in the bladder. Due to their pharmacological action, muscarinic receptor blockers should not be used in people with glaucoma (an eye disease caused by increased intraocular pressure) and in elderly men with difficulty urinating due to prostatic hypertrophy.

In glaucoma, these drugs further increase intraocular pressure, and in prostatic hypertrophy, they can lead to complete cessation of urination (urinary retention). In elderly people, anticholinergic drugs can impair memory.

Stimulators and blockers of nicotinic receptors on ganglion cells (so-called ganglionic stimulators and blockers)

Nicotinic receptors in the autonomic nervous system are located on **ganglion cells** and are distinct from nicotinic receptors on striated muscles. Their activation by ganglionic stimulants (nicotine, lobeline, dimethylphenylpiperazinium /DMPP/, trimethylammonium) leads to complex responses, which are a mixture of activation of the sympathetic and parasympathetic nervous systems. In higher doses, however, these drugs lead to desensitization of nicotinic receptors, and actually blockade of ganglion cells.

On the other hand, the use of drugs that only block nicotinic receptors (**mecamylamine, hexamethonium, trimetaphan**) leads to immediate cessation of activity of both the sympathetic and parasympathetic parts of the autonomic system. The main effects in the body are: tachycardia, orthostatic hypotension / hypotension that occurs when the patient goes from a sitting position to a standing one; due to ganglionic blockade, the baroreceptor reflex does not function/, urinary retention, constipation, decreased salivary secretion, mydriasis and cycloplegia. Given the poor selectivity of nicotinic receptor blockers (hexamethonium, mecamylamine, etc.), they are rarely used in practice. The only clinical application has been found by the ganglionic blocker trimetaphan, which is used to induce controlled hypotension during neurosurgical interventions. The extremely short half-life of trimetaphan (measured in minutes) allows for precise control of blood pressure by simply regulating the rate of intravenous infusion.

However, the use of trimetaphan is not without risk. In some patients, it can potentiate neuromuscular blockade, and in others, it can lead to histamine release and anaphylactoid reactions..

EYE PHARMACOLOGY

With drugs in the eye, we affect several things: the width of the pupil, the tone of the ciliary muscle and the pressure of the aqueous humor. All three things are normally under the control of the autonomic nervous system. Parasympathetic fibers lead to a narrowing of the pupil (miosis), a spasm of the ciliary muscle and an accelerated outflow of aqueous humor through the angle between the iris and the cornea (and thus a decrease in pressure). Activation of sympathetic fibers causes the pupil to dilate (mydriasis) and an increase in the production of aqueous humor in the ciliary body by acting via the beta2-receptor (thereby increasing the pressure of the aqueous humor).

When we want to examine the fundus or measure the refractive power of the eye (e.g. to determine the diopter) it is necessary to dilate the pupil and relax the ciliary muscle (so that the lens bulges out as much as possible). This is achieved by using muscarinic receptor blockers in drops: atropine, homatropine or tropicamide. Homatropine and tropicamide have a much shorter duration of action than atropine, whose effect can last up to a week! The pupil can also be dilated (but without affecting the ciliary muscle) by using the alpha-receptor agonist phenylephrine.

Atropine is also used in inflammation of the iris or ciliary body (iridocyclitis), to occasionally cause mydriasis, and thus prevent the formation of fibrin adhesions (synechiae) between the iris and the cornea or ciliary body. Since blood flow in the eye is accelerated during inflammation, atropine is absorbed quickly, so its effect lasts only a few hours instead of 7 days. Thus, by applying atropine 3 times a day, the iris expands and contracts as many times during the day: we jokingly call this "iris gymnastics".

Glaucoma is an eye disease characterized by pain and retinal damage due to increased pressure in the eye. In acute glaucoma (so-called angle-closure glaucoma), the cause of the sudden increase in eye pressure is the iris moving closer to the cornea, which makes it difficult for the aqueous humor to drain. In this case, a muscarinic receptor agonist should be urgently applied in drops, which will lead to miosis and contraction of the ciliary muscle, separate the iris from the cornea and facilitate the outflow of aqueous humor. The most commonly used muscarinic receptor agonist for this purpose is the alkaloid pilocarpine. An indirect cholinergic drug, physostigmine, can also be used, which, by blocking acetylcholinesterase, leads to the accumulation of acetylcholine on the receptors.

Chronic glaucoma (so-called open-angle glaucoma) is most likely caused by increased production of aqueous humor, resulting in a permanently elevated pressure. The drugs of choice for chronic glaucoma are the β2-receptor blockers timolol and betaxolol. They reduce the production of aqueous humor and thus lead to a decrease in intraocular pressure. When using them, care should be taken not to use them too often, as otherwise they may cause side effects on the lungs and heart (bronchospasm and bradycardia).

The alpha 2 adrenergic receptor agonist brimonidine lowers intraocular pressure by a dual mechanism: it reduces aqueous humor production by the ciliary body and increases its outflow by increasing uveoscleral blood flow. Brimonidine alone can lower intraocular pressure by 23 to 27% from baseline. It is administered topically as eye drops. In addition to beta-blockers and alpha-agonists, the carbonic anhydrase inhibitors dorzolamide and brinzolamide are used to reduce aqueous humor production. Dorzolamide is administered topically as eye drops (20 mg/ml) three times daily; it can lower intraocular pressure by 5 mmHg. Unfortunately, it causes conjunctivitis in about 7% of patients. Brinzolamide is also administered as eye drops; Among the side effects, it causes conjunctivitis and sometimes blurred vision.

Another group of drugs can be used to lower intraocular pressure in open-angle glaucoma, usually in patients who have not responded to or cannot tolerate other drugs. These are synthetic prostaglandin F2alpha analogues, latanoprost, bimatoprost and travoprost. They are applied as eye drops, diffuse through the cornea into the interior of the eye and are broken down there to the active form. They increase the outflow of the aqueous humor by a still unknown mechanism. They are used once a day and are somewhat more effective than timolol and betaxolol. Side effects of latanoprost are conjunctivitis (10% of patients) and a change in the color of the iris (7% of patients). After instillation into the eye, bimatoprost begins to work within 4 hours, and its effect lasts for as long as 24 hours. Compared to latanoprost, bimatoprost causes greater conjunctival hyperemia and iris pigmentation.

Recently, a new drug for chronic glaucoma, **ripasudil**, has appeared, which acts as an inhibitor of the **Rho kinase ROCK**. Rho are GTP-binding proteins, and their substrate is the Rho kinases ROCK 1 and 2, enzymes that, through several interactions, ultimately lead to the polymerization of actin fibers. Due to the inhibition of the Rho kinase ROCK, ***ripasudil blocks the polymerization of actin***, which makes the endothelial cells in the trabecular meshwork of the iridocorneal angle become more flexible, and the space between them increases, which leads to increased swelling of the aqueous humor. Ripasudil is currently used in the form of eye drops (0.4%) together with prostaglandin analogues, and enhances their effect on lowering intraocular pressure. In terms of efficacy, i.e., maximum reduction of intraocular pressure, it does not lag behind other anti-glaucoma drugs. Of the side effects, the only one recorded so far is conjunctival hyperemia. Similar to ripasudil is **netarsudil**, which in addition to inhibiting Rho kinase ROCK blocks noradrenaline uptake; it is also used as an eye drop for the treatment of chronic glaucoma, and causes conjunctival hyperemia as a major side effect..

EICOSANOIDS

Eicosanoids are substances that are formed from polyunsaturated fatty acids with 20 C atoms, and especially from arachidonic acid (Greek εικοσι = twenty). Under the action of phospholipase A2, arachidonic acid is released from the phospholipids of cell membranes. Three enzymes can further act on free arachidonic acid:

1. cyclooxygenase, which catalyzes the formation of prostaglandins, thromboxanes (TXA2) and prostacyclins;
2. lipoxygenase, which catalyzes the formation of trihydroxy-eicositetraenoic acids (lipoxins, LXA and LXB) or leukotrienes (LTB4, LTC4, LDT4 and LTE4).
3. cytochrome P450 reductase, which catalyzes the formation of epoxides (5,6-oxido-, 8,9-oxido-, 11,12-oxido- and 14,15-oxido-eicositetraenoic acid)

Effects on tissues. Eicosanoids act on membrane receptors that are bound to G-proteins. Prostaglandins E and F have the most pronounced effects. PGE2 and PGE1 act on a large number of smooth muscles: they dilate blood vessels, contract longitudinal and relax circular muscles of the digestive tract, contract smooth muscles of the uterus and relax smooth muscles of the bronchi. PGE1 and PGE2 increase body temperature and increase the release of pituitary hormones (growth hormone, TSH,

ACTH, FSH and LH). PGF2alpha and TXA2 have a vasoconstrictor (mainly on veins) and bronchoconstrictor effect. PGF2alpha contracts smooth muscles of the digestive tract and uterus.

TXA2 promotes platelet aggregation, while prostacyclin (PGI2) inhibits aggregation and causes vasodilation.

LTB4 is an extremely potent chemotactic agent for neutrophils. LTC4 and LTD4 are potent bronchoconstrictors, causing increased capillary permeability and increased mucus secretion in bronchial glands. Leukotrienes are thought to be the main mediators that play a role in the development of bronchial asthma (they were once collectively called "slow-reacting substances"). LXA and LXB inhibit the cytotoxicity of natural killer cells and act chemotactically.

Indications for the use of eicosanoids. PGE2 and PGF2alpha are used to prepare the cervix for abortion, as well as to induce abortion in the first and second trimesters of pregnancy.

PGI2 (epoprostenol) is used to treat pulmonary hypertension, and PGE1 and PGI2 are used to treat Raynaud's syndrome and peripheral arteriosclerosis.

PGE1 is used to maintain a patent ductus arteriosus in newborns before cardiac surgery (for transposition of the great arteries, pulmonary atresia, etc.).

Misoprostol (an analogue of PGE1) is used to prevent and treat stomach ulcers caused by the use of nonsteroidal anti-inflammatory drugs, and to induce or stimulate labor. It has cytoprotective effects, and in higher doses it reduces HCl secretion.

PGE2 and PGI2 are used to prevent organ rejection in transplantation because they inhibit the proliferation of T and B lymphocytes.

Adverse effects of prostaglandins are an extension of their pharmacological effects. They most commonly cause nausea, vomiting, and diarrhea. Prostaglandin E1 causes hypotension, flushing, and headache. PGF2alpha in higher doses can cause severe pulmonary hypertension or a jump in blood pressure in the systemic circulation.

HISTAMINE AND ANTIHISTAMINES

Histamine is a biogenic amine that is produced in the body by decarboxylation of the amino acid histidine, under the action of the enzyme histidine decarboxylase. It is synthesized and deposited in the secretory granules of mast cells (in tissues) and basophilic leukocytes (in the blood), together with a large number of other mediators, as an inactive complex with proteases and heparin sulfate or chondroitin sulfate. In addition, histamine is also a neurotransmitter in the central nervous system.

Histamine can be released from the cells in which it is deposited in two ways: by the action of antigens on IgE antibodies on the membrane of these cells, as part of a type 1 allergic reaction, or by a non-exocytotic mechanism, when various drugs, poisons or physical agents damage the membrane of cells containing histamine, or cause histamine to be released from the granules. Drugs and other substances that can lead to histamine release by a non-exocytotic mechanism include: morphine, codeine, guanethidine, d-tubocurarine, iodinated contrast agents, bradykinin, neurotensin, somatostatin, substance P, polymyxin B, anaphylatoxins from complement, and basic polypeptides and phospholipase A from insect venom.

When released, histamine exerts the following effects: vasodilation (of arterioles, capillaries and venules), increased capillary permeability, edema, redness of the skin, itching, contraction of the smooth muscles of the respiratory tract, gastrointestinal and genitourinary tract. All of the above effects are achieved by histamine through the activation of H1 receptors. In addition to H1 receptors, there are H2 receptors through which histamine also causes vasodilation, has a positive inotropic and chronotropic effect on the heart, then increases the secretion of hydrochloric acid in the stomach and reduces its further release from mast cells and basophils. In the central nervous system, H1 receptors are important for maintaining wakefulness, and both H1 and H2 receptors participate in the regulation of blood pressure, body temperature, fluid homeostasis and the processing of pain sensations. In recent years, the existence of H3 and H4 histamine receptors has been shown. All types of histamine receptors, from 1 to 4, belong to the superfamily of G-protein-coupled receptors; H1 receptors lead to calcium mobilization via phospholipase S, H2 receptors increase the concentration of cAMP, and H3 and H4 receptors reduce the entry of calcium into neurons by closing neuronal-type calcium channels in the membrane. H3 receptors are located on the endings of sympathetic nerve fibers and axons of many neurons in the CNS, where when activated they reduce the release of neurotransmitters. Histamine is also found in the venoms of many insects and in many plants or bacteria, so when humans come into contact with them, histamine can enter the body and cause its effects.

Currently, drugs that competitively block H1 and H2 receptors have found clinical application. H1 antihistamines are mainly used for their anti-allergic effect. There are two generations of H1 antihistamines. First-generation drugs are **ethanolamine derivatives** (diphenhydramine, dimenhydrinate), **ethylenediamine derivatives** (pyrilamine, tripelennamine), **alkylamines**

(chlorpheniramine, cyclizine, meclizine, hydroxyzine) and **phenothiazines** (promethazine, cyproheptadine). These drugs are lipophilic, so they are well absorbed, penetrate the CNS and are metabolized in the liver by hydroxylation. Metabolites are excreted in the urine, so the half-life is usually 4-6 hours. First-generation H1 antihistamines block vasodilation caused by histamine, reduce capillary permeability and the sensation of itching (reduce stimulation of nerve endings). Due to their passage into the CNS, they cause sedation. Many of the first-generation antihistamines have antimuscarinic effects; phenothiazines also block alpha adrenergic receptors, and cyproheptadine also blocks serotonin receptors. The most important side effects of first-generation H1 antihistamines are **sedation and antimuscarinic** effects (dry mouth, constipation, urinary retention, accommodation paralysis). In case of poisoning (taking doses of antihistamines many times higher than recommended), symptoms similar to atropine poisoning occur: initially excitation, hallucinations, dry mouth, mydriasis, facial flushing, urinary retention, tachycardia, and later convulsions and coma. First-generation H1 antihistamines alleviate the symptoms of allergic reactions (allergic rhinitis, urticaria, anaphylactic reactions), can prevent the onset of motion sickness, have a beneficial symptomatic effect in Meniere's syndrome (dizziness due to increased endolymph pressure in the semicircular canals) and can be used as hypnotics.

Second-generation H1 antihistamines are water-soluble drugs, piperidine derivatives, that penetrate poorly into the CNS and cause very mild sedation. Loratadine, desloratadine, cetirizine and fexofenadine are eliminated relatively slowly, so their effect lasts up to 24 hours. Loratadine and desloratadine are metabolized in the liver by cytochrome CYP3A4, while cetirizine and fexofenadine are not metabolized, but are excreted unchanged in the urine (cetirizine) and feces (fexofenadine). These drugs block histamine-induced vasodilation, reduce capillary permeability and the sensation of itching (reduce stimulation of nerve endings). In addition, second-generation antihistamines inhibit the release of a large number of inflammatory mediators, by a mechanism that does not involve blocking the H1 receptor. Therefore, in addition to treating allergic manifestations (allergic rhinitis, urticaria, anaphylactic reactions), they are also used as additional drugs for bronchial asthma, especially if it is accompanied by rhinitis, urticaria or dermatitis. The group of second-generation H1 antihistamines once included terfenadine and astemizole; however, these two drugs blocked potassium ion channels (K+) in the myocardium, prolonged the QT interval in the ECG and caused potentially fatal ventricular tachycardia, torsades de pointes. This was especially pronounced in people who were also taking other drugs, cytochrome CYP3A4 inhibitors, which led to a spike in plasma concentrations of terfenadine or astemizole. Today, terfenadine and astemizole are banned for use in many countries.

In addition to the indications already mentioned, H1 antihistamines are also used to treat severe forms of vomiting in the first trimester of pregnancy (hyperemesis gravidarum). The basis for this use of H1 blockers is the existence of functional H1 receptors in the vomiting center (see the chapter "Emetics").

H2 receptor blockers (cimetidine, ranitidine, famotidine) are used to treat peptic ulcer (see the chapter on peptic ulcer therapy), gastroesophageal reflux and Zollinger-Ellison syndrome (hypersecretion of acid in the stomach due to tumors of the endocrine cells of the pancreas that secrete gastrin). These drugs are also used in the treatment of anaphylactic reactions, together with H1 antihistamines. **Cromolyn and nedocromil** are drugs that prevent the release of histamine and other inflammatory mediators from mast cells. In addition, they inhibit the functioning of eosinophils, neutrophils, monocytes, and some neurons. These drugs are used as inhalations to prevent bronchial asthma attacks, and as nasal and eye drops to treat allergic rhinitis and conjunctivitis.

SEROTONIN (5-HYDROXYTRYPTAMINE)

Serotonin is an amine that is formed first by hydroxylation and then by decarboxylation of the amino acid tryptophan. Serotonin is found in a number of neurons of the central (nn. raphe, hypothalamus, pituitary, limbic system) and peripheral nervous system, where it performs the function of a neurotransmitter. The largest part of serotonin can still be found in the endocrine (argentafine) cells of the gastrointestinal mucosa (90%) and platelets (6%). It is metabolized by the action of mono-aminooxidase and aldehyde dehydrogenase to 5-hydroxyindoleacetic acid.

Serotonin causes contraction of smooth muscles of the digestive tract, vasodilation in skeletal muscles and the heart, vasoconstriction in other organs, thickening of the endocardium in the right side of the heart, increased platelet aggregation, and stimulation of pain sensory nerve endings and chemosensitive afferent fibers of the vagus nerve in the coronary circulation. This amine exerts its effects through specific receptors of which there are 7 types: 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7. A number of these types are actually a set of multiple receptor subtypes designated by the letters: A, B, C, D, and E (for example, 5-HT1A, 5-HT1D, etc.). The 5-HT1 receptor has 5 subtypes, and the 5-HT2 receptor has 3 subtypes.

Serotonin itself has no therapeutic use, but some agonists and antagonists of certain subtypes of its receptors are clinically very useful. The 5-HT1_D receptor agonist, **sumatriptan**, has shown excellent efficacy in stopping migraine attacks. Subcutaneous administration of 6 mg of sumatriptan stops migraine attacks in up to 70% of patients. In addition to sumatriptan, drugs with the same mechanism of action and effect have come into use: zolmitriptan, naratriptan, rizatriptan and almatriptan. All are used to

stop migraine attacks, while only sumatriptan is used to stop cluster headache episodes. An inconvenient feature of these drugs is the possibility of coronary spasm, so they must be avoided in patients with coronary disease.

Buspirone, a 5-HT1A agonist, shows anxiolytic activity without causing sedation.

Drugs that block 5-HT2 receptors have an antipsychotic effect, i.e., they belong to the so-called atypical antipsychotics: quetiapine, aripiprazole, ziprasidone and olanzapine.

Tegaserod is a partial agonist of the 5HT4 receptor; acting on this subtype of serotonin receptors on sensory neurons, it causes the release of other neurotransmitters (e.g., calcitonin gene-related peptide). In the digestive tract, tegaserod stimulates peristalsis, increases secretion and inhibits the sensitivity of the intestinal wall. It has been shown to be effective in the treatment of irritable bowel syndrome in women with constipation. The main side effect of tegaserod is diarrhea.

On the other hand, 5-HT3 receptor blockers, **ondansetron and granisetron**, are used as antiemetics in the administration of cytostatics. They are particularly effective if administered immediately before cytostatic therapy - they completely prevent acute vomiting. The non-selective 5-HT receptor blocker, cyproheptadine, also blocks H1 histamine and muscarinic receptors. It is used to treat carcinoid syndrome (excessive production and secretion of serotonin in endocrine tumors of the gastrointestinal tract), dumping syndrome after Billroth 2 gastric resection, and cold urticaria.

CENTRAL NERVOUS SYSTEM (CNS) PHARMACOLOGY

NEUROTRANSMITTERS IN THE CNS

Millions of neurons that make up the central nervous system communicate with each other via neurotransmitters. A complete list of these substances is not yet complete, but some of its members are very well studied.

Dopamine. Dopamine is a catecholamine, which is synthesized from the amino acid tyrosine. Tyrosine enters the nerve ending by active transport, and then in the cytosol under the action of tyrosine hydroxylase is converted into dihydroxyphenylalanine (DOPA). DOPA is further converted into dopamine by the action of DOPA decarboxylase. Dopamine is released at their endings by neurons arranged in well-defined pathways (dopaminergic pathways). The nigrostriatal pathway (neuron bodies are in the substantia nigra and axon terminals in the corpus striatum) is important for the basic control of movement within the extrapyramidal system. Its damage leads to the appearance of Parkinson's disease (muscle rigidity, hypokinesia and tremor). The meso-limbic and meso-cortical dopaminergic pathways (neuron bodies are in the mesencephalon and their axons end in the limbic system, i.e., the cerebral cortex) show increased activity in patients suffering from schizophrenia. The tubero-infundibular dopaminergic pathway (located in the hypothalamus) tonically inhibits the release of prolactin from the anterior pituitary. Dopamine binds to its specific receptors in the CNS, of which there are five subtypes (D1, D2, D3, D4 and D5). All subtypes of dopamine receptors belong to the superfamily of G-protein-coupled receptors. After acting on receptors, dopamine (like the other catecholamine noradrenaline) is taken up into nerve endings and surrounding cells where it is broken down by monoamine oxidase (MAO, especially type MAO-B) and catechol-O-methyl transferase (COMT).

Noradrenaline. Noradrenaline is the second catecholamine with neurotransmitter properties in the CNS. The largest number of neurons containing noradrenaline is concentrated in the locus ceruleus, a small formation in the brainstem. The axons of these neurons reach practically all parts of the CNS. The activity of noradrenergic neurons is reduced in patients with major depression and increased in anxiety states. Noradrenaline binds mainly to alpha-receptors in the CNS, but there are also functional beta-receptors. Noradrenaline plays an important role in the processes of learning, memory and the regulation of the sleep-wake cycle.

Acetylcholine. Neurons that use acetylcholine as a transmitter are present in the corpus striatum, medial septal nucleus and reticular formation. One part of them is organized into the striato-nigral pathway (neuron bodies are in the corpus striatum and axons end in the substantia nigra). This pathway is part of the extrapyramidal system that controls the basis of voluntary movements. Cholinergic neurons are also important for thought processes and memory; cholinomimetics (drugs that mimic the effects of acetylcholine) have been shown to improve the condition in Alzheimer's dementia. Acetylcholine binds to nicotinic and muscarinic receptors in the CNS.

Serotonin (5-hydroxytryptamine). Serotonin is a neurotransmitter of neurons whose bodies are located in the raphe nuclei, the central structure of the pons and the mesencephalon. Their axons extend into almost all parts of the CNS where they exert a mainly inhibitory effect. It is believed that serotonergic pathways regulate the cyclic alternation of wakefulness and sleep, normal body temperature, sexual activity and appetite. Some types of depression are associated with reduced activity of serotonergic

neurons. After being released from nerve endings, serotonin binds to specific serotonin receptors (there are 7 subtypes of these receptors). Its effect ceases due to its uptake into nerve endings and metabolization under the action of monoamine oxidase.

Aminoacids as neurotransmitters

Gamma-aminobutyric acid (GABA). GABA is found in interneurons distributed throughout the CNS. It is formed from glutamate by decarboxylation. It is an inhibitory transmitter that mainly acts on the presynaptic terminals of excitatory neurons and prevents the release of their transmitters. GABA binds to its GABA-A receptors (which are chloride ion channels) or to GABA-B receptors (receptors coupled to G-proteins that affect the opening of potassium ion channels), leading to the opening of ion channels and hyperpolarization of the membrane. GABA-A receptors consist of 5 subunits that span the cell membrane, between which there is a chloride ion channel. Hyperpolarized nerve endings cannot release their transmitters stored in vesicles. Drugs that potentiate the action of GABA (benzodiazepines and barbiturates) lead to a decrease in the activity of the entire central nervous system, sedation and drowsiness. After acting on its receptors, GABA is re-uptaken into nerve endings. In the cytoplasm, it is inactivated by the action of GABA-transaminase. GABA receptors can be blocked by **bicuculline**, a plant alkaloid that causes convulsions in humans, **picrotoxin** and **pentylenetetrazole**. GABA-A receptor agonists are **muscimol and gaboxadol**. A selective GABA-B receptor agonist is **baclofen**.

Glycine. Glycine is also an inhibitory neurotransmitter, but it acts on the postsynaptic membrane. Neurons with glycine are found in the largest number in the spinal cord, and by their role they belong to interneurons. They reduce the activity of neurons that participate in the reflex arc of spinal reflexes. Therefore, the blockade of glycine receptors with strychnine leads to the development of convulsions and tetanic contractions of striated muscles. Tetanus toxin prevents the release of glycine.

Glutamate and aspartate. These two amino acids are excitatory neurotransmitters and are found in neurons present in all parts of the CNS. Most of the normal functions of the CNS are carried out with the help of these neurotransmitters. Glutamate and aspartate bind to two types of receptors: ionotropic (which belong to the superfamily of ion channel receptors) and metabotropic (which belong to the superfamily of G-protein-coupled receptors). Ionotropic receptors are divided into NMDA (N-methyl-d-aspartate is a selective agonist) receptors and non-NMDA receptors (receptors to which the selective agonists kainate and AMPA bind). The intravenous anesthetic ketamine and the hallucinogenic substance phencyclidine also bind to NMDA receptors. There are 8 subtypes of metabotropic receptors, which are classified into three groups. Through ionotropic receptors, glutamate and aspartate cause rapid effects in the cells they act on (within a few milliseconds), and through metabotropic receptors, slower effects (within 30 to 60 seconds).

Peptide neurotransmitters

A large number of peptides have been found in the CNS (**substance P, vasoactive intestinal polypeptide [VIP], enkephalins, endorphins, and others**), but their neurotransmitter role has not yet been proven. **Substance P** (an 11-amino acid peptide) is a neurotransmitter in the Edinger spinothalamic pathway that transmits pain information (it is released at the endings of small unmyelinated nerve fibers in the gelatinous layer of the posterior horns of the spinal cord). It has also been observed that in the neurological disease Huntington's chorea, the concentration of substance P in the substantia nigra is reduced. Vasopressin and oxytocin, two nonapeptides, are found in nerve endings in the neurohypophysis. They act both as neurotransmitters and as hormones. As neurotransmitters, they inhibit neurons in the neurohypophysis; The physiological significance of this inhibition is unknown. As hormones, they act on distant organs. Oxytocin contracts smooth muscle cells of the uterus and myoepithelial cells of the mammary glands, and relaxes smooth muscle cells of the fallopian tubes. **Vasopressin (also known as antidiuretic hormone**) facilitates water absorption in the collecting ducts of the kidneys and constricts blood vessels of the gastrointestinal tract.

Endogenous opioid peptides have also been discovered in the brain, which bind to opioid receptors (μ, kappa, and delta). They are formed by the breakdown of a large protein, proopiomelanocortin. Opioid peptides include **beta-endorphin** (30 amino acids), **leucine- and methionine-enkephalin** (5 amino acids each), and **dynorphin A and B** (8 amino acids each). Endogenous opioid peptides control the sensation and perception of pain.

Imidazoline receptors

Imidazolidine is a pentacyclic ring with two nitrogen atoms in it. Initially, it was thought that there was a group of receptors to which compounds with an imidazolidine ring in them selectively bind, so such receptors were called "imidazolidine". Later, it was understood that other compounds also bind to these receptors, but the name "imidazoline" remained. There are three subtypes of imidazoline receptors: I1, I2 and I3. I1 receptors are important for the effect of central antihypertensive drugs, such as **moxonidine and rilmenidine**. Activation of I2 receptors leads to a decrease in pain perception and reduced neuronal death in the central nervous system. There are currently no drugs with an effect on these receptors on the market, but the substance CR4056 [2-phenyl-6-(1H-imidazol-1yl) quinazoline] is being tested, which has shown a strong analgesic effect in animals. I3 receptors are located on ATP-sensitive potassium channels in pancreatic β-cells, and are involved in insulin secretion..

Blood-brain barrier

There is a barrier between the blood and neurons in the CNS that drugs and endogenous substances must cross in order to reach the neurons from the blood. This barrier is called the blood-brain barrier. It consists of the endothelial cells of the brain capillaries and the extensions of astrocytes that surround the capillaries. The endothelial cells of the brain capillaries are tightly connected to each other and do not have pores, so substances from the blood must pass **THROUGH** the endothelial cells to reach the neurons.

Liposoluble substances, i.e., drugs that are not very ionized at the blood pH of 7.4, easily pass through the endothelial cells by diffusion. Water-soluble substances can only cross the blood-brain barrier if they use the transport mechanism for endogenous substances, by which endothelial cells supply the brain with necessary substances (e.g., transporters for glucose, amino acids GABA, glycine, glutamate, aspartate, purines). Due to the large number of transport mechanisms that require energy, endothelial cells are extremely rich in mitochondria.

In some parts of the brain, the blood-brain barrier does not exist (the capillaries are permeable), which allows neurons to directly "sense" the presence of certain substances in the blood. These areas are the chemoreceptor zone in the area postrema (under the floor of the 4th ventricle), the preoptic recess, and parts of the floor of the 3rd ventricle near the pituitary gland.

The blood-brain barrier is not sufficiently developed in the fetus and newborn, so many drugs easily penetrate the CNS during this period of life.

SEDATIVES AND HYPNOTICS

Sedatives and hypnotics are drugs that reduce the general activity of the CNS; depending on the dose, they can reduce this activity to a greater or lesser extent. In small doses, they only cause sedation, in larger doses they cause drowsiness and sleep, and in toxic doses they put the patient in a coma. They are given to patients who are anxious, usually for a short period of time (7-10 days). Longer use is not desirable, because the patient becomes accustomed to and dependent on them, and his basic problem - the cause of anxiety - is not solved.

Today, the most commonly used sedatives are **benzodiazepines**. They are named after their chemical structure: the skeleton of the molecule is made up of a benzene ring (benzo-) to which a heterocycle with two nitrogen atoms is attached (-diazepines).

Benzodiazepines bind to their receptors in the CNS (which are actually parts of the GABA receptor) and facilitate the action of gamma-aminobutyric acid (an inhibitory transmitter in the CNS, by increasing the frequency of opening of the GABA receptor - the chloride channel); thereby leading to increased inhibition and depression of CNS activity. Since benzodiazepines bind to a different site on the GABA receptor than GABA itself, and affect the binding of GABA to its part of the receptor, such an effect is called allosteric modification. Substances from the beta-carboline group bind to the same benzodiazepine receptor, which act opposite to benzodiazepines: they hinder the action of GABA. Because of this action, beta-carbolines are called inverse agonists, which cause anxiety and convulsions in experimental animals.

The first benzodiazepine to enter widespread use was **chlordiazepoxide**. More than 2,000 benzodiazepines have been synthesized so far, of which about thirty are used as medicines. The most commonly used in our country are **diazepam,**

lorazepam, **bromazepam, alprazolam, clonazepam and midazolam**. Benzodiazepines are relatively safe drugs to use - even in very large, toxic doses, they rarely lead to complete CNS depression and death. However, if taken together with alcohol or another sedative, the depressive effect is additive and can be fatal. The specific antidote for benzodiazepine poisoning **is flumazenil**, a drug that blocks the benzodiazepine receptor.

Benzodiazepines reduce anxiety, but patients ***are also slowed down and drowsy***. Higher doses lead to relaxation of striated muscles and sleep. No matter how much we increase the dose of benzodiazepines, we will not be able to deepen the patient's unconsciousness to the point where breathing or heart function stops. Because of such a wide therapeutic range, or safety, benzodiazepines are today the sedatives of choice.

The main indications for the use of benzodiazepines are patient agitation (anxiety) and insomnia. In addition to sedation and hypnotic effects, benzodiazepines also cause relaxation of striated muscles (only diazepam has a clinically significant effect), so they can be used to treat spasticity. There is no significant difference among benzodiazepines in terms of sedative effect, but when it comes to hypnotic effect (inducing sleep), nitrazepam, flurazepam and temazepam are most commonly used. In addition to being sedatives, diazepam and lorazepam are used to terminate status epilepticus, in the form of intravenous injection. During endoscopic procedures, patients are often given midazolam, a benzodiazepine that is eliminated from the body faster than others (because it is water-soluble), in order to induce the so-called "conscious sedation", i.e., calming the patient while performing these unpleasant examinations. Midazolam also (like all other benzodiazepines) causes anterograde amnesia (the person who takes it does not remember later what happened in the next hour or two) so that the patient agrees to repeated examinations.

Benzodiazepines are also successfully used to suppress the withdrawal syndrome in alcoholics.

Benzodiazepines should be avoided during pregnancy: teratogenic effects have been described! If a pregnant woman uses them in the last month of pregnancy, the child will develop a withdrawal syndrome after birth (anxiety, crying, feeding problems, rarely convulsions). The most common side effects of benzodiazepines are **drowsiness, poor motor coordination, confusion and memory loss**. Less common are hallucinations, blurred vision, paradoxical excitation and gastrointestinal problems.

Benzodiazepines are metabolized in the liver; most are first oxidized by cytochromes and then conjugated with glucuronic acid. Exceptions to this rule are lorazepam, which is directly conjugated, and clonazepam, which is directly acetylated. According to the duration of action (which depends on the rate of metabolism and the activity of the metabolites), benzodiazepines can be divided into: (1) long-acting – chlordiazepoxide, diazepam and flurazepam; (2) intermediate-acting – lorazepam, clonazepam, alprazolam, temazepam; and (3) short-acting – midazolam and triazolam.

Benzodiazepines should be used in lower doses in patients with chronic respiratory insufficiency (risk of respiratory depression) and in patients over 65 years of age. They should not be prescribed to patients with severe liver insufficiency, as they can provoke encephalopathy.

Tolerance develops to benzodiazepines, and patients become psychologically and physically dependent after prolonged use of these drugs. If benzodiazepines are abruptly discontinued, a withdrawal syndrome occurs, consisting of the following symptoms: insomnia, anxiety, tremor, muscle weakness, nausea, hyperalgesia, and convulsions (rarely). Withdrawal syndrome can be prevented by first switching the patient to equivalent doses of diazepam (because its half-life is long), and then reducing the daily dose by about 10 to 20% per week, until the administration is completely discontinued.

To avoid the development of tolerance and dependence on benzodiazepines, it is recommended that patients do not use them for more than 4 weeks when treating insomnia, or for more than 8 weeks when treating anxiety.

In practice, it is very important not to forget that benzodiazepines have an additive depressant effect on the CNS with many other drugs: alcohol, other sedatives, antipsychotics, antihistamines, antiepileptics, opioids and antidepressants.

Until the advent of benzodiazepines, the most widely used sedatives and hypnotics were barbiturates. After binding to their special site on the beta subunit of the GABA receptor (subtype "A") in the central nervous system, they, like benzodiazepines, potentiate the action of GABA, but in a different way. They act by prolonging the time for which the chloride channel (GABA receptor) is open. In addition to acting on GABA A receptors, barbiturates prevent the release of glutamate and block its receptors. The main effects of barbiturates are: sedative, hypnotic, anesthetic and anticonvulsant.

Phenobarbital, pentabarbital and other barbiturates are significantly more dangerous to use than benzodiazepines. If given in a sufficiently large dose, they lead to depression of the lower parts of the CNS (cardiovascular and respiratory centers) and death. Barbiturate poisoning (suicidal and homicidal) is otherwise very common. There is no antidote, but measures that support the work of the heart and lungs are used (infusions of physiological solutions, artificial ventilation).

Today, barbiturates are rarely used as sedatives and/or hypnotics, because benzodiazepines are equally effective and much safer to use. The main use of barbiturates with a longer effect (lasting several hours) is in the prevention of epileptic seizures and the treatment of febrile convulsions in children (phenobarbital is most often used for these purposes). A short-acting barbiturate (thiopentone sodium) is used for short-term intravenous anesthesia or for induction of general inhalation anesthesia.

Barbiturates are metabolized in the liver, first by oxidation on cytochromes, and then by conjugation. According to the duration of action, they can be divided into: (1) long-acting - phenobarbital; (2) medium-acting - amobarbital and butabarbital; (3) short-acting - pentabarbital and secobarbital; and (4) ultra-short-acting - thiopentone sodium.

Side effects of barbiturates are excessive sedation, depression, weakening of thought processes and memory, then the appearance of nystagmus, ataxia (cerebellar symptoms) and dependence (physical and mental). They also accelerate the metabolism of many drugs (and thus their elimination from the body) because they induce the synthesis of monooxygenase in the liver. They are contraindicated in people with hepatic porphyria (a disorder in heme synthesis) because they accelerate the formation of toxic heme precursors.

In addition to benzodiazepines and barbiturates, other substances also exhibit sedative and hypnotic effects: chloral hydrate, meprobamate, glutethimide, etchlorvinol, and others. However, since they have more side effects and no advantages over benzodiazepines and barbiturates, they are used extremely rarely.

Two drugs that have a different chemical structure than benzodiazepines can bind to benzodiazepine receptors: **zolpidem, zopiclone, and zaleplon**. Although they bind to the same receptors, they modulate the action of GABA differently, so their effects differ somewhat from those of benzodiazepines. They cause sedation and hypnosis, but they have weaker anxiolytic, muscle relaxant, and anticonvulsant effects than benzodiazepines. Due to their short duration of action, these drugs are used as hypnotics, especially for insomnia in which falling asleep is a problem. Patients do not have problems with hangovers the next day. The half-life of zaleplon is only 1 hour, zolpidem 2-3 hours, and zopiclone 5 hours. In practice, hypnotics should be prescribed for a maximum of 3-4 weeks; insomnia must be permanently treated for its cause.

A new hypnotic with a different mechanism of action is **daridorexant**. Daridorexant blocks both receptors for the neuropeptide **orexin**: orexin receptor 1 (OH1) and orexin receptor 2 (OH2). After administration of this drug, the patient falls asleep quickly, and if he wakes up during the night, he falls asleep again quickly. The patient does not feel a hangover the next day, but he may suddenly fall asleep, similar to what happens in narcolepsy. The main side effects are headache and nasopharyngitis.

Pure anxiolytics separate the sedative effect from the anxiolytic effect. **Buspirone** is one of the relatively new drugs that has been shown to have anxiolytic effects without causing sedation. It binds to serotonin receptors of the 5-HT1A type (on which it acts as a partial agonist), and in order to exert its effect, at least a week must pass from the onset of administration. Buspirone also has no muscle relaxant or anticonvulsant effect.

The use of buspirone is reserved for the treatment of generalized anxiety disorder and anxiety accompanying depression. The most common side effects of buspirone are mild dizziness and headache. It is not addictive.

Table 1. Doses of the most commonly used sedatives (calculated for an adult weighing approximately 70kg).

SEDATIVE	INDICATION	ROUTE OF ADMINISTRATION	SINGLE DOSE	DOSE INTERVAL
Diazepam	Status epilepticus	Intravenous injection (i.v.)	10 mg	The same dose could be repeated after 30-60 minutes
Diazepam	Anxiety	Oral	2 mg	8 h
Nitrazepam	Insomnia	Oral	5 mg	One dose before bed
Midazolam	"Conscious sedation"	i.v.	2 mg	After 2 minutes add 0.5 mg, if necessary

STIMULANTS OF CENTRAL NERVOUS SYSTEM

Stimulation of the central nervous system includes increased alertness, the appearance of anxiety and, if extremely strong, convulsions. Stimulation can occur in three basic ways: by depression of inhibitory neurotransmission in the CNS, by enhancement of excitatory neurotransmission, or by removal of presynaptic control of neurotransmitter release. Drugs that stimulate the CNS can be classified into three groups: **analeptic stimulants, psychomotor stimulants and methylxanthines**.

Analeptic stimulants

This group includes the alkaloids **strychnine and picrotoxin**, and the synthetic substances **doxapram and pentylenetetrazol**. Doxapram, pentylenetetrazol, and picrotoxin bind to a special site on the GABA receptor (the so-called picrotoxin site), and interfere with the action of GABA, which leads to the closure of the chloride channel and depolarization of the neuronal membrane. Strychnine acts in another way: it blocks receptors for the inhibitory neurotransmitter glycine, which are particularly present in the spinal and medulla oblongata. Inhibition of glycine receptors allows for hyperactivity of spinal and bulbar reflexes.

Analeptic stimulants are almost never used as drugs. Only doxapram is sometimes used to relieve respiratory depression after general anesthesia.

All drugs in this group are well absorbed after oral administration, and their effect is short-lived, because they are rapidly metabolized in the liver.

If administered in toxic doses, analeptic stimulants cause **respiratory stimulation, tachycardia, hypertension, tonic-clonic convulsions, and then coma**. Strychnine poisoning looks somewhat different: due to the disinhibition of spinal and bulbar reflexes, the poisoned person reacts to the slightest sound or light stimulation with hyperextension, which in extreme cases turns into opisthotonus. During hyperextension, the patient cannot breathe, so that he is actually suffocating while fully conscious. The benzodiazepines diazepam and clonazepam can somewhat counteract the effects of strychnine.

Psychomotor stimulants

Psychomotor stimulants include amphetamine, methamphetamine, pemoline, and methylphenidate. They act by releasing catecholamines from presynaptic terminals, inhibiting their reuptake, and stimulating dopamine and serotonin receptors.

These drugs are well absorbed after oral administration, are partly metabolized in the liver, and partly excreted unchanged in the urine. Since they are weak bases, their excretion can be increased by forced diuresis and acidification of the urine.

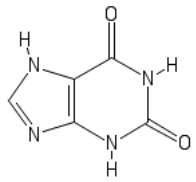
Amphetamine, pemoline, and methylphenidate are used to treat attention deficit/hyperactivity disorder in children (hyperactivity, impulsive behavior, and inability to concentrate). Amphetamine is also effective in the treatment of narcolepsy (a disorder characterized by attacks of daytime sleep, sudden loss of muscle tone – cataplexy, nightmares and flaccid paralysis upon awakening). The drug modafinil, whose mechanism of action is unknown, has also been used successfully to treat narcolepsy.

If these drugs are overdosed, euphoria, tremors, cardiac stimulation, irritability, insomnia, and then convulsions and coma occur. Chronic use of psychomotor stimulants leads to weight loss due to anorexia and a state resembling psychosis.

Psychomotor stimulants cause psychological and physical dependence. Tolerance also develops to them. When long-term use of amphetamine is abruptly discontinued, a withdrawal syndrome occurs, consisting of the following symptoms: prolonged sleep, fatigue, depression and extreme hunger.

Methylxanthines

Methylxanthines have a xanthine nucleus, which is common to purine bases and uric acid.



Ксантинско језгро

Figure 18. Xanthine nucleus.

Three methylxanthines are of pharmacological importance: **caffeine, theophylline, and theobromine**. Caffeine is found in coffee (one cup of coffee contains about 100 mg of caffeine), tea (30 mg per cup of tea), cocoa (a cup of hot cocoa contains 15 mg of caffeine), and Coca-Cola (40 mg per 330 ml). Theophylline is found in tea, and theobromine in cocoa.

Methylxanthines are well absorbed after oral administration. They are metabolized to uric acid derivatives.

Methylxanthines **block A1 adenosine receptors**, thus preventing the inhibitory effect of adenosine on both the postsynaptic and presynaptic membranes. In addition, caffeine acts as an **inverse agonist of benzodiazepine receptors**, thus reducing the permeability of chloride ion channels. All these effects ultimately lead to depolarization of the neuronal membrane and their excitation.

Methylxanthines are used to treat CNS depressant intoxication: a combination of caffeine and sodium benzoate is administered intramuscularly. Theophylline is used to stop attacks of bronchial asthma, in the form of the ethylenediamine salt, known as aminophylline. Aminophylline can be administered parenterally or rectally. Aminophylline is also used to treat pulmonary edema, in the form of an injection. Caffeine, in the form of the citrate salt, is used for the short-term treatment of apnea in premature infants. When aminophylline is administered as an intravenous injection, it must last at least 20 minutes. If administered more quickly, there is a risk of arrhythmias.

Caffeine is also effective in combination with non-opioid analgesics for headache relief, as it causes vasoconstriction of the blood vessels of the brain.

Side effects of methylxanthines are nervousness, insomnia, and delirium after administration of large doses. Extrasystoles and tachycardia occur in the heart. Breathing is accelerated, and urine output is increased.

Caffeine from coffee can be addictive. People who drink more than 6 cups of coffee a day become addicted to caffeine, so if they do not take their usual dose, they get severe headaches and a feeling of fatigue.

ANTIPSYCHOTICS

The term "psychosis" refers to a disorder that can have various causes, but must have the following symptoms: hallucinations, delusions, reduced ability to process information and draw logical conclusions, catatonia, non-purposeful behavior, aggression and loss of associations. Schizophrenia is a type of psychosis, characterized by a chronic course, loss of emotions, withdrawal and a feeling of loss of control over one's thoughts. The symptoms of schizophrenia can be divided into "positive", which actually represent an abnormal increase in normal functions (e.g. agitation), and "negative", which represent a loss of normal functions (e.g. loss of emotions). Negative symptoms are far more resistant to therapy.

It is believed that the biochemical basis of schizophrenia is increased activity of dopaminergic neural pathways: meso-limbic and meso-cortical. Antipsychotics primarily block dopamine receptors on neurons where dopaminergic pathways terminate (all block the D2 receptor subtype). However, blockade of dopamine D4 and 5-HT2 serotonin receptors also contributes to the antipsychotic effect. In addition to the aforementioned receptors, a number of antipsychotics also block muscarinic, alpha-adrenergic, and H1 histaminergic receptors..

Antipsychotics are drugs used to treat schizophrenia, the manic phase of manic-depressive psychosis, and some delusional states. Antipsychotics are classified into 4 chemical classes: **phenothiazines** (which are divided into aliphatic compounds - chlorpromazine, piperidines - thioridazine, and piperazines - fluphenazine), **butyrophenones** (haloperidol), **thioxanthenes** (thiothixene) and others, so-called "**atypical**" or "new" drugs. Atypical antipsychotics (**clozapine, olanzapine, risperidone and its active metabolite paliperidone, quetiapine, ziprasidone, aripiprazole, asenapine, cariprazine**) in addition to binding to D2 dopamine receptors, can block D4 receptors and serotonin receptors, especially the 5-HT2 subtype. Because of this property, these drugs affect a slightly larger number of schizophrenia symptoms than "typical" antipsychotics.

Antipsychotics primarily suppress the so-called "positive" symptoms of schizophrenia: the appearance of delusions, illusions and hallucinations, agitation. The "negative" symptoms of schizophrenia (poor socialization, emotional blunting, deficits in the thought process), unfortunately, respond poorly to these drugs. For the full effect of antipsychotics to manifest, several days or even weeks must pass. About 40% of patients respond poorly to "typical" antipsychotics; in these patients, the use of **clozapine**, which is currently considered the most effective antipsychotic, is indicated..

Due to their non-selectivity, they also block receptors in other dopaminergic pathways. This is the reason for the appearance of their most common side effects: Parkinson's-like syndrome (akinesia, rigidity and tremor), acute dystonia (neck, head, face curvature), akathisia (hypermotility attacks) and tardive dyskinesia (appearance of choreiform movements after several months of therapy) due to blockade of the nigrostriatal pathway; milk secretion (galactorrhea), amenorrhea, gynecomastia and loss of libido in men, and increased libido in women, all due to blockade of the tubero-infundibular pathway and increased secretion of prolactin. Antipsychotics also block muscarinic receptors, and often exhibit unwanted anticholinergic effects: constipation, difficulty

urinating, dry mouth, difficulty sweating, accommodation disorder. To a certain extent, these drugs also block alpha-adrenergic receptors, which leads to postural hypotension and the inability to ejaculate. Antipsychotics also adjust the hypothalamic thermostat to lower values, resulting in hypothermia. By a still unknown mechanism, they cause heart rhythm disorders (especially thioridazine, which causes prolongation of the QT interval), act epileptogenically and in a small number of patients cause hepatitis accompanied by jaundice. A rare, but very serious side effect of antipsychotics is the so-called neuroleptic malignant syndrome. It is characterized by muscle rigor, increased body temperature and hypotension with a tendency to transition to a state of shock. It is treated primarily by discontinuing antipsychotics, a drug that prevents the release of calcium from the sarcoplasmic reticulum (dantrolene), and nonspecific measures to combat acidosis and shock.

Due to the blockade of H1 histaminergic receptors, many antipsychotics (especially phenothiazines) cause sedation, which is why a single daily dose of the drug is taken in the evening, before going to bed.

Antipsychotics cause photosensitization, and can be deposited in the cornea, lens and retina (thioridazine can also cause retinopathy).

Clozapine has a particular tendency to cause **neutropenia**, so it is necessary to monitor the number of leukocytes in the peripheral blood during therapy with this drug.

Atypical antipsychotics differ in their side effects from typical ones. While typical antipsychotics are dominated by motor disorders and side effects due to the blockade of other receptors of the autonomic nervous system, these effects are significantly less pronounced in atypical ones. However, atypical antipsychotics have pronounced **metabolic** side effects: patients experience weight gain (except for aripiprazole), hyperlipidemia, decreased glucose tolerance, hyperglycemia, and even the development of diabetes. Of all atypical antipsychotics, the most pronounced metabolic side effects are caused by clozapine and olanzapine, and the least by aripiprazole (which does not cause weight gain or hyperlipidemia) and ziprasidone. Antipsychotics have another beneficial effect: they prevent vomiting. Together with the opioid analgesic fentanyl, haloperidol is used to induce so-called neuroleptic analgesia, in which it is possible to perform shorter surgical interventions or unpleasant diagnostic procedures; the antipsychotic reduces the patient's emotional reaction to pain.

Choice of antipsychotics

Although there are some clinical studies that claim that atypical antipsychotics are more effective than classic ("typical") ones, there is still not enough evidence to take a definitive position. A characteristic of antipsychotics is that their effect is very individual: one patient responds well to one of the antipsychotics, while he did not respond to others, and another patient, on the other hand, responds only to one of the drugs that had no effect on the first patient. Therefore, for each patient, the antipsychotic that best suits him should be chosen. One should start with one drug, and if it is not effective, switch to another, and so on, until the best solution is found.

When choosing antipsychotics, one should also take into account their tendency to cause side effects, especially when the patient already has an additional disease, such as metabolic syndrome or prolactinemia. Of the atypical antipsychotics, quetiapine has the lowest propensity to cause extrapyramidal syndrome, and risperidone and paliperidone have the highest propensity to cause hyperprolactinemia. Aripiprazole, ziprasidone, asenapine, and paliperidone carry the lowest risk of metabolic syndrome..

Dose regimen of antipsychotics

Patients with schizophrenia almost without exception require continuous therapy with antipsychotics. Multiple antipsychotics should never be combined, as this does not increase efficacy. Antipsychotics can usually be administered in a single daily dose, usually at bedtime. Since there is no correlation between the concentration of antipsychotics in the serum and their effect, dosing is extremely individual; in fact, each patient should start with the lowest doses and increase them until an effect is obtained. Then continue therapy with this determined dose.

Haloperidol, risperidone and olanzapine can be administered parenterally. Parenteral administration is important for calming the symptoms of acute psychosis and delirium, which very often occurs in elderly people after admission to hospital.

Sometimes patients with schizophrenia do not cooperate in taking their medication regularly, making it difficult to achieve disease control. In such situations, instead of oral administration, patients can be given an intramuscular injection of antipsychotics, in the form of a **depot preparation**. In a depot preparation, the antipsychotic is bound to a long-chain fatty acid (e.g. fluphenazine or haloperidol decanoate) or is contained in microscopic balls (microspheres) made of polymers of lactic acid and glycolic acid (poly lactic-co-glycolic acid, e.g. depot preparation of risperidone). The bond between the antipsychotic and the fatty acid is gradually hydrolyzed or the bonds in the polymer of the microspheres are hydrolyzed, and the antipsychotic is gradually released

into the blood. It is sufficient to administer only one injection every 3 weeks, and during all this time the patient has a stable concentration of the drug in the blood.

Table 2. Doses of the most commonly used antipsychotics (calculated for an adult weighing approximately 70kg).

ANTPSYCHOTIC	INDICATION	ROUTE OF ADMINIST RATION	SINGLE DOSE	DOSE INTERVAL
Chlorpromazine	Delirium	Intramuscular injection (i.m.)	50 mg	-
Chlorpromazine	Schizoprenia	Oral	50 mg	8 h
Tjhioridazine	Schizoprenia	oral	50-200 mg	8 h
Flufenazine – decanoat	Schizoprenia	i.m.	25 mg	15 days
Risperidone	Schizoprenia	oral	1-8 mg	24 h

ANTIDEPRESSANTS

Depression is a mood disorder that occurs in a wide range of clinical presentations: in a normal person, it resolves when the event that caused it is removed; in neurotic depression, the causal event is hidden in the patient's subconscious - depression can be cured with psychotherapy, so that the patient eventually becomes aware of the causal event; in psychotic depression (today, the more appropriate names are "major depressive disorder" or "major depression"), there is no causal event, and the cause of the disease is a biochemical disorder of neurotransmission in the central nervous system. Symptoms of depression are: feelings of guilt, self-deprecation, lack of motivation, insomnia, loss of appetite, desire for self-destruction. Major depression can occur as such, or in conjunction with mania (periods of depression are reduced by periods of mania /agitation, good mood inappropriate to the circumstances, irritability, impulsiveness/) as part of the so-called "bipolar psychosis".

Although the biochemical basis of major depressive disorder is still unclear, there is evidence that the activity of noradrenergic and serotonergic pathways in the CNS is reduced (both noradrenaline and serotonin are chemical monoamines, so this view of the cause of depression is called the "monoamine theory"). Antidepressants increase the activity of these pathways by increasing the amount of neurotransmitters near the receptors. They do this in two ways: 1) by blocking the reuptake of mediators (tricyclic antidepressants, heterocyclic / or "atypical" / antidepressants and selective serotonin reuptake inhibitors) or 2) by blocking the breakdown of mediators (monoamine oxidase enzyme inhibitors - MAO). All antidepressants only exert their effect after a latent period of 2-4 weeks, so during this period the patient should be intensively protected from suicide attempts.

A new antidepressant with a completely different mechanism of action than the antidepressants already mentioned has recently entered clinical use: **esketamine**, a derivative of the intravenous anesthetic ketamine. Esketamine works by enhancing the effects of glutamate in the central nervous system..

Tricyclic antidepressants

Imipramine was the first drug in this group to be shown to be effective in suppressing symptoms of depression (in the late 1950s). Later, several other drugs with similar efficacy and chemical structure were synthesized, with three rings in the molecule, all of which are collectively called "tricyclic antidepressants". These are the tertiary amines amitriptyline, imipramine, trimipramine, doxepin, and the secondary amines desipramine, nortriptyline, and protriptyline.

Unfortunately, tricyclic antidepressants exhibit many side effects that are similar to those of neuroleptics due to their chemical relationship to phenothiazines. They have antimuscarinic effects (dry mouth, constipation, difficulty urinating, tachycardia, blurred vision), and in the cardiovascular system they can cause, in addition to tachycardia, postural hypotension (due to alpha1 receptor blockade), and in predisposed individuals, epileptic seizures. Excessive sedation also poses a serious problem in therapy (occurs due to blockade of histamine H1 receptors), especially when it comes to amitriptyline. Blockade of H1 receptors is also the reason for increased appetite and body weight. If overdosed, they cause mania and arrhythmias.

They should never be used with alcohol (they potentiate its depressive effects), hypotensive drugs and MAO inhibitors (hypertensive crisis, hyperpyrexia, convulsions occur). Antipsychotics, oral contraceptives and some serotonin reuptake inhibitors inhibit the metabolism of tricyclic antidepressants in the liver, thereby increasing the concentration of tricyclics in serum.

When tricyclic antidepressants are used, it is necessary to monitor their concentration in the blood, after the equilibrium state is established. The reason for this is that people who metabolize tricyclic antidepressants slowly (due to a deficiency of the appropriate enzymes), of which there are about 5%, can have extremely high concentrations of these drugs in the blood even at usual doses. By measuring the concentration of the drug immediately after the equilibrium state is established, it is possible to detect such people and prevent the occurrence of poisoning by reducing the dose.

Tricyclic antidepressants, in addition to treating depression, are used to treat bedwetting in children, neuropathy, chronic pain, and obsessive-compulsive disorder (the drug of choice here is clomipramine). The mechanism of action in these diseases is unclear.

Heterocyclic antidepressants

In an effort to overcome the aforementioned side effects of tricyclic antidepressants, a large number of new compounds with a slightly different mechanism of action have been synthesized - the so-called heterocyclic ("atypical") antidepressants or second-generation antidepressants (maprotiline, amoxapine, trazodone, nefazodone, mirtazapine, venlafaxine and bupropion). Amoxapine and maprotiline are heterocyclic antidepressants, but their effect and pharmacokinetics are very similar to tricyclic antidepressants. **Maprotiline** has a particularly high tendency to cause convulsions, and **amoxapine**, among other things, also blocks dopamine receptors (acting as antipsychotics). Other heterocyclic antidepressants have significant specificities, such as fewer side effects than others (**venlafaxine**), a **sedative effect (mirtazapine and trazodone**) or causing insomnia (**bupropion**). In addition to treating major depressive disorder, venlafaxine has been used successfully in the treatment of generalized anxiety disorder, panic disorder, and social phobia. **Mirtazapine** is used only for the treatment of depression, but it has no anticholinergic effect, and **does not affect the cardiovascular system**, which makes it a suitable drug for use in the elderly. Although it belongs to the group of antidepressants, bupropion is not currently used to treat depression, but rather as an aid to quitting smoking in people who have become addicted to nicotine. Trazodone is used as an antidepressant, but it is also widely abused due to its hypnotic effect for the treatment of insomnia, and its sedative effect for the treatment of anxiety. In a number of patients, trazodone causes damage to liver cells, and in some men, **priapism** (a prolonged and painful erection that sometimes ends in permanent neurological damage).

Selective serotonin reuptake inhibitors (SSRIs)

Since 1987, a new group of antidepressants has been introduced: selective serotonin reuptake inhibitors (**fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine**). It has not yet been confirmed that serotonin reuptake inhibitors are more effective than classic drugs, but they have been successful in some patients refractory to classic drugs.

These drugs do not block muscarinic, adrenergic, or histaminergic receptors, so they do not have the antimuscarinic and sedative effects of tricyclic antidepressants. They can cause anxiety and insomnia in some patients. Since they often cause gastrointestinal problems, they should be taken with food, as these problems are less severe. Rarely, these drugs can also cause bleeding from the gastrointestinal tract. As many as a third of patients taking SSRIs experience sexual side effects: anorgasmia, erectile dysfunction, delayed ejaculation, decreased libido.

Sometimes SSRIs can cause "**serotonin syndrome**" due to excessive accumulation of serotonin (especially when given together with MAO inhibitors). This syndrome consists of hyperthermia, muscle rigidity, myoclonus, and confusion. Some patients have experienced increased aggression after taking fluoxetine, and a small number have experienced increased suicidal tendencies. Paroxetine causes weight gain in patients and has a sedative, rather than an excitatory, effect.

Fluoxetine and paroxetine are potent, and sertraline is a weak inhibitor of the cytochrome P450 2D6 isoenzyme. Therefore, they can interact with drugs that are metabolized by this isoenzyme, and increase their concentration in the blood, thereby increasing toxicity. Interactions with drugs that have a narrow therapeutic index are especially dangerous: with antiarrhythmics from group 1C (encainide, flecainide, propafenone). Citalopram stands out from other SSRIs by its extremely low potential for inhibiting the P450 2D6 isoenzyme.

Of the selective serotonin reuptake inhibitors, paroxetine has the most pronounced teratogenic effect if used in the first three months of pregnancy.

Monoamine-oxydase inhibitors

There are two types of monoamine oxidase enzymes: MAO-A and MAO-B. MAO-A is a non-selective enzyme and oxidizes all catecholamines in the CNS (dopamine, noradrenaline) and serotonin; MAO-B selectively acts only on dopamine. The first MAO inhibitors blocked the work of both types of enzymes (**iproniazid, tranylcypromine, phenelzine, isocarboxazid**). Later, selective blockers of only MAO-A were synthesized, of which **moclobemide** found clinical application.

MAO inhibitors are effective drugs for endogenous depression, but they are more difficult to use than tricyclic antidepressants. The reason lies in the numerous side effects, smaller therapeutic range and interactions with ingredients of some foods. Side effects are somewhat similar to those of tricyclic antidepressants: drowsiness, antimuscarinic effects (dry mouth, difficulty urinating), postural hypotension, weight gain, sweating and muscle cramps, jaundice. Of particular note is the increased risk of chemical hepatitis. Overdose can lead to delirium, convulsions, hyperthermia and coma. During treatment with MAO inhibitors, the patient should not consume **aged cheese, smoked fish, wine and yeast**. The aforementioned foods contain a lot of tyramine, which acts by releasing catecholamines from nerve endings; since MAO is blocked, tyramine can lead to excessive accumulation of noradrenaline near the receptors and hypertensive crisis.

MAO inhibitors should not be given together with indirect sympathomimetics (ephedrine, amphetamine) and tricyclic antidepressants because hypertensive crisis may occur. Their use together with the opioid **meperidine** is also contraindicated because of the occurrence of hyperpyrexia, hypotension and coma. Due to the pronounced side effects and the possibility of serious interactions, MAO inhibitors are reserved for patients with depression resistant to other antidepressants.

John's wort as an antidepressant

St. John's wort (Hypericum perforatum) is a widely distributed herb with significant medicinal properties. The whole plant (herba), usually dried and crushed, is used in medicine; extracts for human use are usually prepared from the primary herbal material.

Most of the pharmacological effects of St. John's wort are due to **hypericin, flavonoids, and hyperforin**. St. John's wort has antidepressant properties; clinical studies have shown that its effect is similar to that of tricyclic antidepressants in major depressive disorder. However, it is still unclear when St. John's wort should be preferred over other antidepressants.

Esketamine

Esketamine is the S-enantiomer of the intravenous anesthetic ketamine, which modulates the activity of NMDA and AMPA glutamate receptors, and then activates brain-derived neurotrophic factor and mechanistic target of rapamycin (mTOR); the latter two functional proteins help neuron development and synaptic plasticity. It is administered as a nasal spray and has a potent antidepressant effect. For now, it is used only in depression that does not respond to classical antidepressants. The most common side effects of esketamine are dissociation, sedation, dizziness, anxiety, lethargy, a feeling of intoxication and an increase in blood pressure.

Choosing an antidepressant

All antidepressants known to date have similar efficacy, so the choice of drug is made according to the individual characteristics of the patient, side effects and response to the drug. In principle, patients accept serotonin reuptake blockers and newer heterocyclic antidepressants more easily, because they have less sedative effects and fewer antimuscarinic side effects. If the patient does not respond to the first antidepressant, a second, then a third, should be tried until the appropriate effect is achieved. The combination of antidepressants is generally avoided, although there are some clinical studies that have shown a positive effect of the combination of serotonin reuptake blockers with desipramine, bupropion or mirtazepine.

MAO inhibitors have shown a good effect in "atypical" depression (patients with tension, phobias and hypochondriasis).

Antidepressants are usually used for a couple of years, and then their withdrawal is attempted, if the patient is doing well. When stopping antidepressants, it must be done **GRADUALLY**, i.e., by gradually reducing the dose over 2-4 weeks. If antidepressants are stopped abruptly, withdrawal symptoms occur: nausea, lethargy, dizziness and headache..

Finally, we **do NOT** use antidepressants to treat a depressive episode of bipolar disorder, as they accelerate the transition from the depressive to the manic phase. We use lithium, lamotrigine, or ziprasidone to prevent and treat the depressive phase of bipolar disorder.

Table 3. Doses of the most commonly used antidepressants (calculated for an adult weighing approximately 70kg).

ANTIDEPRESSANT	INDICATION	ROUTE OF ADMINISTRATION	SINGLE DOSE	DOSE INTERVAL
Amitryptiline	Major deprssion	oral	75 mg	24 h
Imipramine	Enuresis nocturna	oral	25 mg for children 6-7 years of age	24 h
Trazodone	Major deprssion	oral	150 mg	24 h
Fluoxetine	Major deprssion	oral	20 mg	24 h
Moclobemide	Major deprssion	oral	150 mg	12 h

LITHIUM

Lithium is effective in the body in the form of a lithium ion (Li+), which is similar in chemical properties to the sodium ion (Na+). The mechanism of action is not yet fully understood (it is currently believed to interfere with the hydrolysis of inositol phosphate to inositol, which is otherwise a necessary step for the regeneration of phosphatidyl inositol in the cell membrane, as well as to change the functioning of G-proteins, because it interferes with the binding of magnesium ions), but lithium is very effective in calming the symptoms of mania (it helps in 70% of patients within 5-20 days) and in the prophylaxis of manic-depressive psychosis (i.e. reducing the frequency of manic and depressive episodes).

Lithium is well absorbed after oral administration, and does not bind to plasma proteins. Lithium is eliminated in the urine. Lithium elimination has a biphasic character. In the first 10 hours after taking the dose, elimination is rapid (40% of the dose is eliminated), and then it slows down. Therefore, it is recommended to take blood samples to measure lithium concentration only after 12 hours from the last dose of the drug. The half-life of lithium is 12 to 24 hours.

Since it penetrates all tissues, lithium has many side effects. It causes weight gain, disrupts the thyroid gland (hypothyroidism), causes leukocytosis, and antagonizes the action of antidiuretic hormone in the kidney, leading to excessive excretion of dilute urine. On the skin, it causes acne and can also worsen psoriasis. Due to its effect on the CNS, tremors of the hands and sometimes confusion occur. It is teratogenic!

Lithium is administered orally, in the form of lithium carbonate salt. The therapeutic range is very small (therapeutic plasma lithium concentrations are from 0.5 to 1 mmol/l, and toxic ones are already above 1.5 mmol/l!), and if the threshold of toxic doses is exceeded, the following occur: first vomiting, diarrhea, confusion and ataxia, and later drowsiness, convulsions, coma and arrhythmias. The usual initial dose of lithium carbonate is 200 mg every 6 hours, orally. However, it is necessary to control plasma lithium concentrations during therapy, and adjust the dose accordingly; this is the only way to avoid the occurrence of toxic effects. In order to prevent lithium intoxication, it is very important to maintain the usual sodium intake, and to avoid the use of diuretics, which can lead to hyponatremia. In the event of hyponatremia, lithium toxicity increases, as it enters the cells more than usual.

Instead of lithium, antiepileptics can be used to calm the symptoms of acute mania and prevent manic and depressive episodes in the so-called bipolar disorder: valproic acid, carbamazepine, lamotrigine or topiramate. Due to their simpler administration and somewhat lower toxicity, many doctors prefer them over lithium for this indication.

One of the atypical antipsychotics, **ziprasidone**, is also effective both in calming the patient in an acute manic episode who is agitated (there is an injectable form that is administered parenterally), and in preventing manic and depressive episodes in bipolar disorder (the oral form of the drug is used for this indication).

EPILEPSY AND ANTI-CONVULSANTS

Epilepsy

Epilepsy is a brain function disorder characterized by the occasional and unpredictable occurrence of convulsions, involuntary movements, disturbances of consciousness, behavioral disorders, or sensory disorders. The cause lies in the non-physiological, synchronous activation of a group of neurons, which occurs due to a disruption in the functioning of ion channels in the membranes of neurons. The incidence of epilepsy in the general population is about 0.5%.

All epilepsies can be classified into 2 groups: focal (the old name was “partial”) and generalized.

Focal epilepsies can be simple (consciousness is preserved, involuntary movements or paresthesias occur only in one limb, sometimes the autonomic nervous system is activated) and complex (disorder of consciousness associated with stereotyped behavior, the so-called psychomotor epilepsy). Abnormal neuronal activation remains localized to only one part of the central

nervous system. If the activation spreads to all parts of the central nervous system, focal seizures become generalized (secondarily generalized).

Generalized epilepsies can be characterized by loss of consciousness alone (such a seizure is called absence, from the English word absence, or petit mal, which means "little seizure" in French) or the loss of consciousness is accompanied by contractions of the striated muscles (tonic-clonic seizures /tonic-clonic seizures are also called grand mal, in French "big seizure"/, clonic seizures, tonic seizures or myoclonic seizures). There are also atonic seizures, which are characterized by a sudden loss of tone of the striated muscles.

By the mechanism of occurrence, ***absence*** is different from all other epilepsies. It occurs due to uncontrolled oscillations of electrical impulses between the thalamus and the cerebral cortex. The electroencephalogram shows a characteristic picture: a spike-wave complex, with a frequency of 3 per second. The opening of T-calcium channels in the membrane of thalamic neurons plays a crucial role in the emergence and amplification of these oscillations.

Anti-convulsants

The choice of antiepileptic drugs is based on the type of epilepsy, as most antiepileptic drugs only work on some forms of epilepsy. For the treatment of focal and tonic-clonic seizures, carbamazepine, oxcarbazepine, phenytoin, valproic acid, phenobarbital, lamotrigine, levetiracetam, brivaracetam, zonisamide or topiramate are used. Absence seizures are a specific form of epilepsy, which is only affected by ethosuximide or valproic acid. For atonic and myoclonic seizures, the drugs of choice are valproic acid, clonazepam or levetiracetam. In addition to the above antiepileptic drugs, there are drugs that are mainly used as additional therapy, in addition to the existing "basic" antiepileptic drug: vigabatrin, gabapentin, topiramate.

The majority of patients with epilepsy (70%) can be successfully treated with a single drug, while the rest must be prescribed two or more drugs. Before starting treatment, it is important to accurately determine the type of epilepsy, and then start treatment with the drug of choice, gradually increasing the dose until seizure control is achieved. If seizure control is achieved, the patient then remains on the same drug for a long time, with occasional monitoring of the drug concentration in the serum. If control is not achieved with the first drug, two more drugs should be tried individually; only in the case of therapeutic failure with three individual drugs, the patient should be given a combination of antiepileptic drugs. When replacing antiepileptic drugs, the drug being replaced begins to be gradually discontinued only after the full dose of the new drug has been reached.

A patient who has been introduced to an antiepileptic drug remains on such therapy for at least two years after the last seizure. Only then should the possibility of discontinuation of therapy be considered; if the doctor decides to do so, the discontinuation of therapy must be very gradual, over several months, by gradually reducing the dose.

People with epilepsy may only drive private vehicles, provided that they have been seizure-free for at least a year, or have been seizure-free during wakefulness for at least 3 years.

Carbamazepine and oxcarbazepine act primarily by blocking Na+ channels in neuronal membranes. The blockade is dependent on the activity of the neuron: the more often a neuron generates action potentials, the more of its Na+ channels will be blocked by the drug (hence antiepileptics have a certain selectivity of action, since they act most strongly on abnormally active neuronal groups; this property of antiepileptics is called "use-dependent blockade"). Blockade of Na+ channels stabilizes the resting potential and reduces neuronal excitability. In addition, these two drugs partially block the action of the excitatory neurotransmitter glutamate on NMDA receptors. Carbamazepine and oxcarbazepine have similar side effects, only they are less pronounced in oxcarbazepine. In addition to gastrointestinal complaints, diplopia, drowsiness, confusion, ataxia, generalized erythema, transient leukopenia, and hyponatremia (due to potentiation of the action of antidiuretic hormone) occur. Only carbamazepine induces the synthesis of the isoenzyme CYP3A4, thus accelerating the elimination of drugs that are metabolized by the same isoenzyme. This is especially important for other antiepileptic drugs, oral contraceptives, warfarin, and cyclosporine, whose blood concentration (and thus the effect) decreases significantly if they are administered together with carbamazepine.

In addition to the treatment of epilepsy, carbamazepine and oxcarbazepine are used to treat bipolar disorder and neuropathic pain.

Phenytoin acts on all forms of epilepsy, except for absans. It blocks sodium and calcium channels, and potentiates the action of GABA.

Phenytoin is slowly but completely absorbed from the gastrointestinal tract. It can be administered intravenously, but not intramuscularly, due to improper absorption. Fosphenytoin, a prodrug, is used for intramuscular administration, which is completely converted to phenytoin in the body. Phenytoin is eliminated via metabolism in the liver, and has a saturable character. Saturation of the metabolic pathway occurs already at therapeutic doses, so that the drug concentrations in serum can vary greatly

from patient to patient. This means that the dosing of phenytoin must be very careful, with control of the drug concentration in serum.

The side effects of phenytoin are numerous, and significantly more frequent at higher doses. Tremor, nystagmus, blurred vision, ataxia, confusion, gastrointestinal complaints occur. Gingival hypertrophy, facial features become coarser, acne appears, and in women, hirsutism. Like carbamazepine, it induces the metabolism of other drugs and vitamins. Due to increased degradation, folic acid and vitamin D deficiency occurs, and megaloblastic anemia and osteomalacia occur. It also accelerates the metabolism of warfarin and cyclosporine. In addition to the treatment of epilepsy, phenytoin is also used to treat neuropathic pain and arrhythmias.

Newer antiepileptics that affect sodium ion channels are **zonisamide** (blocks sodium channels) and **lacosamide** (modulates sodium channels so that they accelerate their closure). They are used as additional therapy for partial epilepsies, which is facilitated by the fact that they interact poorly with other antiepileptics. Zonisamide is more toxic, as it causes confusion, a higher incidence of renal calculi, and oligohidrosis in children (difficulty sweating). Lacosamide causes only dizziness and diplopia, but therefore has significant teratogenic potential if used in the first trimester of pregnancy.

Valproic acid and its salts, such as sodium valproate, have the broadest spectrum of action of all antiepileptics: they have a beneficial effect on all known types of epilepsy. This is due to the multiplicity of their mechanism of action: they block sodium channels, potentiate the action of GABA, block T-type calcium channels and block the action of glutamate on NMDA receptors. Due to its slow penetration into neurons, valproic acid achieves a therapeutic effect only after a latent period of several weeks.

Side effects of valproic acid and its salts include gastrointestinal complaints, rarely pancreatitis, weight gain due to appetite stimulation, transient alopecia and curly hair growth, thrombocytopenia, tremor, ataxia and confusion. In the early stages of therapy, valproic acid can cause severe chemical hepatitis (this is especially common in children under 3 years of age). Therefore, liver function (serum transaminase levels) must be monitored frequently during valproic acid administration. Valproic acid inhibits the metabolism of some antiepileptic drugs, increasing their blood concentrations: phenobarbital, lamotrigine, and the active metabolite of carbamazepine. In addition to the treatment of epilepsy, valproic acid and its salts are used for the treatment of neuropathic pain, bipolar disorder, and the prophylaxis of migraine attacks.

Lamotrigine is a selective drug that blocks sodium ion channels only on neurons that use glutamate and aspartate as transmitters. Thanks to this action, lamotrigine can prevent partial and generalized seizures. Some of the side effects of lamotrigine are similar to those of carbamazepine: rash, drowsiness, diplopia, ataxia, headache, tremor. However, lamotrigine has one specific side effect: it causes a flu-like syndrome, most likely due to its effect on prostaglandin synthesis. In addition, it is extremely important to know that lamotrigine must be introduced into therapy gradually, i.e., from the lowest to the recommended maintenance dose, over a period of 2 months. Otherwise, if the recommended maintenance dose is started immediately, Stevens-Johnson syndrome (the appearance of bullae on visible mucous membranes and skin) may occur.

Phenobarbital and primidone are effective against all types of epilepsy, except for absence seizures. Both drugs potentiate the effect of GABA on GABA-A receptors; primidone is partially transformed into phenobarbital in the body. Primidone is used less and less, because it has no advantages over phenobarbital, and it has more side effects.

Similar to carbamazepine and phenytoin, phenobarbital can cause sedation, fatigue, and confusion. In the elderly, paradoxical excitement may occur, and in children, hyperactivity. It leads to folic acid deficiency, because it accelerates its metabolism in the liver. Phenobarbital also accelerates the metabolism of many drugs, which leads to the loss of their therapeutic effect (e.g., other antiepileptic drugs, cyclosporine, warfarin, oral contraceptives). It causes psychological and physical dependence.

For the treatment of absence seizures, drugs are used that selectively block T-channels for calcium in the membrane of thalamic neurons. These **are succinimides (ethosuximide) and oxazolidinediones (trimethadione)**. Ethosuximide has very few side effects (nausea and anorexia), so today it has completely replaced the more toxic trimethadione from use. In addition to absence seizures, ethosuximide also has a beneficial effect on **myoclonic seizures, tonic and atonic seizures**. The drug is well absorbed after oral administration, but is slowly metabolized in the liver by cytochrome CYP3A4 (half-life 3 days).

Recently, drugs have been synthesized that can control resistant forms of epilepsy. **Gabapentin** is usually used together with Na+ channel blockers to control resistant partial epilepsies. Gabapentin increases the release of GABA from presynaptic terminals. In addition to treating partial seizures, gabapentin is also used to treat neuropathic pain. Gabapentin may cause drowsiness, ataxia, fatigue, diplopia, tremor, and impaired glucose tolerance.

Vigabatrin increases GABA concentrations by irreversibly blocking GABA-transaminase, the enzyme that breaks it down. It is also used only as an adjunct (to a primary antiepileptic drug) in the treatment of epilepsy. Vigabatrin has a serious adverse effect on the retina: it leads to visual field defects. Therefore, its use is currently limited to those patients who do not respond to other antiepileptic therapy.

The drug **tiagabine** has a very special mechanism of action. Tiagabine **blocks the reuptake of GABA** into neurons and glial cells, thereby increasing its concentration and effect, especially in the thalamus and hippocampus. In practice, it is used to treat **partial seizures**, together with some other antiepileptic drugs. Sometimes it causes tremors, impaired concentration and lethargy.

In clinical practice, the most effective of the new antiepileptic drugs has been **topiramate**, which acts by blocking sodium channels, blocking AMPA receptors for glutamate and potentiating the effect of GABA.

Topiramate has proven to be an effective monotherapy for partial, then generalized tonic-clonic seizures, Lennox-Gestaut syndrome and West syndrome. The drug is relatively well tolerated; Most side effects occur in the first 4 weeks: drowsiness, fatigue, impaired thinking, confusion. After prolonged use, **kidney stones** have been observed in some patients. It reduces sweating, so in the summer it can lead to hyperthermia. It can also cause acute glaucoma. Topiramate can also be used for the prophylaxis of migraine attacks.

Two other antiepileptic drugs act by blocking glutamate receptors: **felbamate, which blocks NMDA** receptors, and **perampanel, which blocks AMPA** receptors. While perampanel is used for both partial and generalized epilepsies, felbamate is used only for partial epilepsy and Lennox-Gastaut syndrome that are unresponsive to other antiepileptic drugs because of its potentially fatal side effects (aplastic anemia and fulminant hepatitis). Perampanel can cause **aggression,** anger, irritability, and homicidal ideation.

Levetiracetam is used as monotherapy or in combination with other antiepileptic drugs for the treatment of partial epilepsy with and without secondary generalization, myoclonic seizures, and tonic-clonic seizures. Levetiracetam binds to synaptic vesicles and impairs the process of exocytosis. It causes emotional lability, insomnia, anxiety, aggression, and anorexia in patients. A derivative of levetiracetam with the same mechanism of action **is brivaracetam.**

Only a few years ago, the drug **ezogabin**e (also known as retigabine) entered clinical practice, which acts by opening potassium channels, leading to hyperpolarization of the neuronal membrane. It is effective in the treatment of partial epilepsy with and without secondary generalization. Ezogabine has two specific side effects: it causes **urinary retention and bluish pigmentation** of the nails, skin, lips, and retina.

Perampanel is also a newer antiepileptic drug that blocks AMPA receptors for the excitatory amino acids glutamate and aspartate. It is used to treat focal and generalized epilepsy. It has pronounced psychiatric side effects, so attention should be paid to this when prescribing this drug: irritability, aggressiveness, intrusive thoughts of suicide or killing another person.

All of the aforementioned antiepileptic drugs are actually used in the prevention of epileptic seizures. When a seizure does occur, it usually lasts for a short time and ends spontaneously. Sometimes, however, the seizure can last for over 5 minutes, and the patient is said to be entering status epilepticus. This condition must be interrupted because uncontrolled muscle contractions cause serious metabolic disorders (lactic acidosis, hyperkalemia) that can endanger the patient's life. Benzodiazepines - **diazepam or lorazepam** - are used for termination in the form of intravenous injections. They potentiate the effect of GABA and thus interrupt the synchronous discharge of neurons. If it is not possible to provide an intravenous route of administration, the seizure can be terminated by rectal administration of a micro-enema with diazepam or by administration of **midazolam** into the gingivo-buccal sulcus.

If status epilepticus does not stop after 30 minutes of benzodiazepine administration, **phenytoin, fosphenytoin, or phenobarbital** can be administered intravenously, with mandatory ECG monitoring. Fosphenytoin has an advantage over phenytoin and phenobarbital because it is dissolved in water, while the other two drugs are dissolved in propylene glycol, which can cause heart rhythm disturbances after intravenous administration. If status epilepticus does not stop after 60 minutes of second-line drugs, the patient should be put under general anesthesia with the intravenous anesthetics thiopentone sodium, midazolam, or propofol.

Table 4. Doses of the most commonly used antiepileptic drugs
(calculated for an adult weighing approximately 70kg)

ANTICONVULSANT	INDICATION	ROUTE OF ADMINISTRATION	SINGLE DOSE	DOSE INTERVAL
Carbamazepine	Grand mal	oral	200 mg[1]	6 h
Ethosuximide	Petit mal	oral	250 mg for children < 6 years	24 h
Phenobarbital	Partial epilepsy	oral	150 mg	24 h
Phenytoin	Grand mal	oral	100 mg	8 h
Valproic acid	Myoclonic seizures	oral	5 mg /kg for children < 20 kg[2]	6 h

1. Therapy begins with lower doses (50 mg/6 hours), and these are gradually increased to the specified maintenance dose.
2. This dose can be gradually increased to 10 mg/kg/6 hours, but only with transaminase control and occasional measurement of the drug concentration in serum.

Interactions between anticonvulsants

Since antiepileptics are sometimes combined, there is a possibility of interactions between them. Carbamazepine, phenobarbital and phenytoin are potent inducers of liver microsomal enzymes, so they reduce the blood concentration of antiepileptics administered together with them. On the other hand, valproate inhibits the metabolism of phenobarbital and lamotrigine (leading to an increase in their blood concentration), and displaces phenytoin from its connection with plasma proteins, leading to an increase in the concentration of the free fraction of the drug in the blood (and thus enhancing the effect of phenytoin).

Anticonvulsants in pregnancy

All antiepileptic drugs have teratogenic effects, but they must still be used during pregnancy, because an epileptic seizure poses a very high risk to the mother and child. Among them, **lamotrigine and levetiracetam** are the least teratogenic, but they can also cause cleft lip and/or palate. Carbamazepine and valproic acid cause neural tube defects in 2 to 4% of pregnancies, which can be partially prevented by the use of folic acid before and during pregnancy. Lacosamide has also been shown to be a significant teratogen. In pregnant women taking antiepileptic drugs, the level of alpha-fetoprotein in the blood should be measured and an ultrasound examination of the fetus should be performed in the second trimester, in order to detect possible anomalies.

During pregnancy, the concentration of antiepileptic drugs in the mother's blood can drop significantly, especially in the second half of pregnancy. Therefore, it is necessary to measure the concentration of antiepileptic drugs and adjust the dose according to the results obtained.

When the mother is taking phenytoin, carbamazepine or phenobarbital, there is an increased risk of bleeding in the newborn. Therefore, prophylactic vitamin K should be given to the mother before delivery (at 36 weeks) and to the newborn.

Breastfeeding is possible with most antiepileptic drugs with strict follow-up, except for phenobarbital or some newer antiepileptic drugs.

Anticonvulsants for bipolar disorder

In the treatment of **acute mania**, the therapy of choice is a combination of **lithium and one of the atypical antipsychotics**. To reduce the frequency and depth of mood swings in bipolar disorder, lithium or one of the antiepileptics (valproate, carbamazepine or lamotrigine) are used.

The mechanism of action of antiepileptics in bipolar disorder remains unclear. They are thought to reduce the brain's sensitivity to mood swings, which is why they are called "mood stabilizers".

The recommended dose of valproate for this indication is 1.5-2 g per day, while carbamazepine is given at a dose of about 1 g/day, orally. Lamotrigine must be introduced into the therapy gradually, starting with a minimum dose of 25 milligrams, which can be increased up to 400 milligrams per day.

In manic patients refractory to therapy with lithium or antiepileptic drugs alone, a combination of lithium with valproate, carbamazepine, or lamotrigine may be used..

THERAPY OF PARKINSON'S DISEASE

A neurological disease that manifests itself with a triad of symptoms (tremor, muscle rigidity, and bradykinesia) was first described by James Parkinson in 1817; the disease was later called Parkinson's disease or Parkinsonism. Parkinsonism occurs as a result of damage to the nigrostriatal dopaminergic pathway, as neurons in the substantia nigra die. In these neurons, Lewy bodies (composed of cytoskeletal proteins, alpha-synuclein, ubiquitin, and synaptophysin) and the dark pigment neuromelanin first accumulate in the cytoplasm, and then the cells die. Usually the cause of the damage is unknown, but sometimes it is not. For

example, when heroin is manufactured improperly, the preparation is contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MFTP), which destroys dopaminergic neurons in users of this drug and causes the clinical picture of severe parkinsonism (the so-called "frozen addict"). As already mentioned, Parkinson's disease manifests itself in motor disorders: muscle **rigidity** that has a "gear" character when the stiff limb is stretched, **tremor at rest** (the patient makes characteristic movements with the fingers of the hand "as if counting money") and **hypokinesia** (the face becomes "like a mask", the voice changes, the patient does not swallow saliva regularly, so it leaks out of the mouth). There are two basic approaches to treating this disease.

1) Improving the activity of the dopaminergic nigrostriatal pathway.

L-dopa. Dopamine itself cannot be used as a drug because it has significant peripheral effects and poorly penetrates the CNS. Therefore, the precursor of dopamine, the amino acid l-dopa, is used. L-dopa is well absorbed in the gastrointestinal tract, using active transport for neutral amino acids. However, as much as 90% of orally administered l-dopa is broken down in the intestinal wall under the action of dopa-decarboxylase. To prevent this, l-dopa is used together with inhibitors of this enzyme: **carbidopa or benserazide**. L-dopa is converted into dopamine in the brain without hindrance because dopa-decarboxylase inhibitors do not penetrate the blood-brain barrier. L-dopa penetrates the blood-brain barrier using the same active transport for neutral amino acids.

The side effects of l-dopa are mainly due to the non-selective activation of other dopaminergic pathways in the brain. Since dopaminergic receptors are present in the vomiting center and the chemoreceptor zone connected to it, the administration of l-dopa is often accompanied by vomiting. Due to the activation of the meso-limbic and meso-cortical pathways, hallucinations, nightmares and confusion may occur. Finally, an overdose of the drug produces dyskinesias: involuntary and purposeless movements. Sometimes the "on-off" phenomenon occurs: the patient suddenly falls into complete immobility ("off"), only to recover spontaneously after a short time ("on"). The mechanism of this phenomenon is not yet known.

Special problems with the use of l-dopa are postural hypotension, cardiac arrhythmias (because the dopamine produced by l-dopa activates beta1 receptors in the heart) and the fact that its effectiveness is lost after 2-3 years of therapy.

L-dopa should not be given together with sympathomimetics and non-selective MAO inhibitors, because hypertensive crisis may occur. Also, the drug is contraindicated in patients with narrow-angle glaucoma, because due to the mydriasis it causes, it can provoke an attack of glaucoma.

Since amino acids from food compete with l-dopa for active transport in the intestinal epithelium, they can interfere with the absorption of this drug. Therefore, l-dopa should be given before meals, at least half an hour.

Bromocriptine, apomorphine, pergolide, ropinirole and pramipexole. These drugs are dopaminergic receptor agonists. They are used in the treatment of early forms of Parkinsonism (usually given to younger patients whose intellect is preserved), or in advanced forms of the disease in which the nigrostriatal pathway has already completely degenerated, and the effect of L-dopa has weakened. Side effects are similar to those of L-dopa (postural hypotension, fatigue, drowsiness, dyskinesias, hallucinations, confusion). In addition to the treatment of parkinsonism, bromocriptine is also used to stop breastfeeding, or to treat pituitary tumors that secrete prolactin or somatotropic hormone (because it suppresses the release of prolactin). While older drugs in this group (bromocriptine, pergolide, and apomorphine) act on D1 and D2 dopamine receptors, newer drugs (pramipexole and ropinirole) are selective agonists of D2 receptors. Therefore, newer drugs have fewer side effects (e.g., they do not cause retroperitoneal fibrosis).

In addition to the aforementioned side effects, bromocriptine can cause peripheral artery spasm, and bromocriptine and pergolide can also cause retroperitoneal fibrosis. Apomorphine, due to its action on opioid receptors, can also lead to respiratory depression.

While all other drugs in this group are administered orally, **apomorphine and rotigotine** are administered parenterally. Apomorphine is given as a subcutaneous injection or subcutaneous infusion in patients with advanced disease to suppress periods of “offness,” i.e. reduced mobility. It is rapidly metabolized in the liver, so its effect is short-lived. Rotigotine is administered as a transdermal patch.

Monoamine oxidase B (MAO-B) inhibitors. Dopamine is broken down in neurons by the enzyme monoamine oxidase-B. The selective MAO-B inhibitors, **selegiline and rasagiline**, increase dopamine levels in the brain without affecting norepinephrine levels. Selegiline and rasagiline are used as monotherapy in the early stages of Parkinson's disease (because they have a moderate effect but very few side effects) and as adjunctive therapy with some of the previous drugs in refractory forms of Parkinson's disease (e.g., with L-dopa). They prolong the use of L-dopa and reduce the required doses of that drug. Unlike rasagiline, selegiline is metabolized to methamphetamine and amphetamine, so it can cause insomnia if given in the afternoon or evening.

Recently, it has been shown that MAO-B inhibitors may be able to slow the progression of parkinsonism to some extent and improve the quality of life of people with parkinsonism, but definitive confirmation of these beneficial effects is still awaited.

There is experimental evidence that selegiline increases the synthesis of antiapoptotic proteins and antioxidants in neurons, which may indicate a neuroprotective effect of this drug.

Amantadine. Amantadine increases the release of dopamine from nerve terminals and prevents its reuptake. It is less effective than other drugs and tolerance to its effects occurs quickly. It is used mainly in patients who no longer respond to first-line drugs. Side effects of amantadine include: confusion, insomnia, hallucinations, livedo reticularis (reticular erythema of the skin), and orthostatic hypotension.

Entcapone is an inhibitor of the enzyme catechol-O-methyltransferase (COMT), which breaks down a third of the amount of levodopa in the body. It does not pass through the blood-brain barrier, so it acts only on the periphery, increasing the amount of L-dopa that will reach the central nervous system. It is administered together with L-dopa, and slows down its breakdown. Among the side effects, it causes hallucinations, dyskinesias and abdominal pain.

2) Decreased activity of the cholinergic striato-nigral pathway, which normally has the opposite effect on motor function than the nigrostriatal pathway.

Blockers of muscarinic receptors that penetrate the CNS can improve some symptoms of parkinsonism, primarily tremor, while they have little effect on bradykinesia and rigidity. Trihexyphenidyl, biperiden, benzatropine and procyclidine are less effective than dopaminergic drugs, but can be useful when the effect of l-dopa "wears off". They have classic antimuscarinic side effects: amnesia, dry mouth, constipation, difficulty urinating, accommodation paralysis, difficulty sweating, etc. In addition, they cause confusion, hallucinations and memory impairment. They are well absorbed after oral administration, and are metabolized in the liver.

Table 5. Doses of the most commonly used antiparkinsonian drugs
(calculated for an adult weighing approximately 70kg)

ANTIPARKINSONIAN DRUG	ROUTE OF ADMINISTRATION	SINGLE DOSE	DOSE INTERVAL
L-dopa + benserazide	oral	100 mg + 25 mg	6 h
Selegilin	oral	10 mg,	24 h
Bromocriptin	oral	2.5 mg [1]	12 h
Trihexyphenidyl	oral	2 mg [1]	6 h

1. Therapy begins with lower doses (1 mg/24 hours), and these are gradually increased to the specified maintenance dose.

Treatment of Parkinson's disease in younger people usually begins with selegiline or amantadine, and then switches to dopamine receptor agonists. In the elderly, L-dopa is the drug of first choice, because it rarely causes confusion, which especially interferes with daily functioning in older people. When L-dopa begins to lose its effect after a few years, amantadine, entacapone or selegiline can be added. Apomorphine can be administered parenterally in states of "disconnection" of the patient, and quickly help him (bring him to a mobile state). Antimuscarinic drugs are especially used in patients who, due to hypokinesia of the pharynx and infrequent swallowing, saliva leaks from the mouth; by reducing saliva secretion, they reduce the severity of this unpleasant problem.

TREATMENT OF ALZHEIMER'S DISEASE

Alzheimer's disease is a type of dementia characterized by cognitive decline (difficulty thinking) and memory loss. It affects about 10% of people over 65 years of age. Beta-amyloid and Tau proteins accumulate in the cerebral cortex (especially in association regions), hippocampus, amygdalae, and subcortical nuclei, and neurons fail to function. Amyloid is formed from a transmembrane precursor protein that is cleaved into fragments by the enzymes beta and gamma secretase; the most important fragment is beta-amyloid protein, which forms oligomers, which then aggregate to form amyloid. Tau protein normally stabilizes microtubules and enables the transport of neurotransmitter vesicles in neurons. In Alzheimer's dementia, Tau protein becomes hyperphosphorylated and forms aggregates in the form of a network of fibers..

Reversible acetylcholinesterase inhibitors (**tacrine, rivastigmine, donepezil, galantamine**) are still used in the treatment of Alzheimer's disease, but their effectiveness has been shown to be low. They can slow cognitive decline in about 50% of patients, but at most for a few months. **Galantamine**, in addition to inhibiting acetylcholinesterase, also activates nicotinic receptors. These drugs can cause cholinergic side effects: bronchospasm, bradycardia, diarrhea, sweating, miosis, etc. Rivastigmine has an advantage over other acetylcholinesterase inhibitors, because it is not metabolized in the liver, so it does not interact with other drugs. **Memantine, a blocker of the NMDA** receptor for glutamate, is used with significantly greater success in the treatment of Alzheimer's dementia today. Memantine is a derivative of amantadine. The most important side effects are constipation, hypertension and drowsiness.

Every 6 months, it should be checked whether further cognitive decline has occurred despite the use of the drug. If so, further therapy is discontinued. Memantine can also be combined with an acetylcholinesterase blocker.

A few years ago, two monoclonal antibodies for the treatment of mild Alzheimer's disease were also approved for sale: **aducanumab and lecanemab**. These monoclonal antibodies bind to amyloid and remove it from the central nervous system. The clinical effect of these monoclonal antibodies is reduced to a minimal improvement in cognition. In almost 40% of patients, they cause edema and microbleeds in the brain in places where there was amyloid, so monitoring of patients with magnetic resonance imaging is necessary.

Intensive research is underway into new drugs that could prevent the progression of the disease by preventing the formation of beta-amyloid and fibrils made of Tau protein, or by removing beta-amyloid through an immune mechanism. None of these drugs have yet been registered for the treatment of this serious disease, as clinical studies have not shown favorable results. In 2020, China approved a drug for Alzheimer's disease with a completely new mechanism of action. The drug has the code name **GV-971**, and it is an oligosaccharide from seaweed that normalizes the disturbed bacterial flora in the large intestine. It was previously discovered that the disturbed intestinal flora activates certain subsets of T-lymphocytes, which then penetrate the central nervous system and cause inflammation there.

TREATMENT OF MULTIPLE SCLEROSIS

Multiple sclerosis is an autoimmune inflammatory disease that leads to demyelination of neurons in the central nervous system and a variety of neurological disorders. Changes are visible in the white matter of the brain on magnetic resonance imaging. In most patients, the disease has a course characterized by alternating exacerbations and improvements (relapses and remissions). After many years of such a course, in most patients the disease becomes progressive, without remissions (the so-called secondary-progressive form), and leads to bedridden patients and urinary and fecal incontinence. A smaller number of patients have the so-called primary progressive form from the beginning.

It has long been believed that T-lymphocytes are the main factors in the development of inflammatory lesions in multiple sclerosis, but in recent years great progress has been made in understanding the role of B-lymphocytes. It has been shown that drugs that reduce the number and activity of B lymphocytes are more effective in treating multiple sclerosis than drugs that target T lymphocytes. That is why the order of drug administration in patients with multiple sclerosis has been changed.

Primary therapy for multiple sclerosis has long involved the use of **interferon beta 1 (a or b)** in the form of subcutaneous injections three times a week. This drug can cause **depression with suicidal thoughts** in a number of patients, and in some it can lead to the development of **nephrotic syndrome or liver damage**. Most patients develop a flu-like syndrome after the injection. The effectiveness of interferon beta 1 is not high: it reduces the frequency of disease relapse from 3 in two years to 2 in two years, and slows the progression of neurological deficit by about twenty percent.

Now, instead of interferon beta 1, the monoclonal antibodies **ocrelizumab and ofatumumab** are used in the primary therapy of both relapsing-remitting and primary progressive multiple sclerosis, which bind to the CD20 receptor on B lymphocytes and lead to the destruction of lymphocytes that have this receptor on them. As a result, the migration of B lymphocytes into the central nervous system, antigen presentation to T lymphocytes, and inflammation with damage to nervous tissue are reduced. Ocrelizumab and ofatumumab are far more effective than interferon beta 1; ocrelizumab is administered intravenously only once every 6 months, and ofatumumab once a month, as a subcutaneous injection. The main side effect of both drugs is an increase in the frequency of infections, especially viral (e.g. herpes).

Glatiramer, a drug that resembles a myelin protein, can also be used in primary therapy. Glatiramer leads to the **accumulation of T-helper lymphocytes type 2 in the central nervous system**, which then secrete anti-inflammatory cytokines there. The drug is administered as a subcutaneous injection once a day, and similar to interferon beta 1, reduces the frequency of relapses and somewhat slows the progression of neurological deficits. Redness and pain often occur at the injection site, and sometimes atrophy of subcutaneous fat tissue. Some patients experience a feeling of suffocation, a rapid heartbeat, and a flushed face after taking glatiramer. Recently, oral multiple sclerosis drugs have also been included in primary therapy: **teriflunomide and dimethyl fumarate**. **Teriflunomide** inhibits mitochondrial dihydroorotate dehydrogenase, which is necessary for pyrimidine synthesis, resulting in a decrease in the number of lymphocytes in the blood. The clinical effect of teriflunomide is similar to that of interferon beta 1. Like other antimetabolites, it leads to **bone marrow suppression**, increased frequency of infections, hair loss, diarrhea, and sometimes liver damage. In addition, it increases blood pressure. **Dimethyl fumarate** increases the synthesis of antioxidants in cells. The efficacy and side effects of dimethyl fumarate are very similar to the efficacy and side effects of teriflunomide. In patients who do not respond well to first-line therapy, **natalizumab**, a monoclonal antibody against integrins on the leukocyte membrane, is used as a secondary therapy. It prevents the adhesion of T-lymphocytes to endothelial cells and thus their arrival at sites of demyelination in the central nervous system. It is administered as an intravenous infusion every 4 weeks. The efficacy of natalizumab is greater than that of interferon beta 1 (it reduces the frequency of relapses and the progression of neurological deficits to a greater extent), but it has one serious side effect: it increases the risk of progressive multifocal leukoencephalopathy in people infected with the John Cunningham virus. Therefore, the use of natalizumab is not recommended if this infection is present, and periodic testing for the presence of antibodies to the aforementioned virus in the blood of patients receiving natalizumab is advised.

As a secondary therapy for multiple sclerosis, sphingosine-1-phosphate receptor blockers are also used, which lead to its internalization and degradation. As a result, lymphocytes enter the central nervous system less. **Fingolimod, siponimod, ponesimod** are administered orally. In terms of efficacy, they are between interferon beta 1 and natalizumab. Among the side effects, they increase the frequency of respiratory infections and lead to bradycardia and A-V block.

Mitoxantrone (an antitumor antibiotic that interferes with the functioning of DNA, primarily in cells that divide intensively, and thus reduces the number of lymphocytes that reach the central nervous system), **cladribine** (an antimetabolite that is incorporated into DNA and blocks DNA polymerase, leading to a decrease in the number of lymphocytes) and **alemtuzumab** (a monoclonal antibody against the CD52 antigen on the lymphocyte membrane, which leads to the destruction of these cells and thus reduces inflammatory activity in the central nervous system) are also used in the secondary therapy of multiple sclerosis. Mitoxantrone is administered once every three months, and cladribine and alemtuzumab once a year. The effectiveness of these drugs is similar to that of natalizumab, but they have more side effects. Mitoxantrone and cladribine have side effects typical of cytostatic drugs, and alemtuzumab increases the frequency of infections (prophylaxis against herpesvirus infections with acyclovir must be used), causes a flu-like syndrome after injection and can lead to the development of various autoimmune diseases.

When patients with multiple sclerosis relapse despite the above therapy, **short-term (so-called "pulse") therapy with high-dose corticosteroids** is used: 1 gram of methylprednisolone per day, for 3-5 days, in the form of intravenous infusion or injection. This therapy should stop the inflammation and accelerate recovery, but this does not happen in all patients. High doses of corticosteroids lead to transient sodium and water retention and edema.

TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis is a degenerative disease that is based on the degeneration of motor neurons. The disease is incurable, so the median survival is about 3 years. A drug that can prolong survival by at least a few months is **riluzole.** Riluzole **reduces the excitotoxic effect of glutamate** on motor neurons and thus slows down their degeneration, but the precise mechanism of action is still unknown. Riluzole is administered orally, and as a liposoluble drug penetrates the central nervous system where it acts, and is then metabolized in the liver by cytochromes to inactive metabolites. The most important side effect of riluzole is an increase in serum aminotransferases.

Another drug that can slow the progression of amyotrophic lateral sclerosis has recently been approved: **edaravone**. Edaravone is an antioxidant that is administered intravenously, daily for 15 days a month; the patient is off treatment for the next 15 days, until the beginning of the following month.

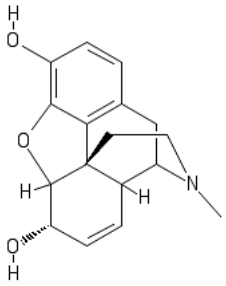
The **antisense oligonucleotide tofersen** is indicated for the treatment of patients with amyotrophic lateral sclerosis who have a mutation in the superoxide dismutase 1 gene. Tofersen binds to the RNA that carries information from the mutated superoxide dismutase 1 gene, thus preventing the synthesis of the altered and toxic enzyme. Tofersen is administered into the cerebrospinal fluid (intrathecally) by lumbar puncture, once a month.

OPIOIDS

For centuries, opium, the juice obtained by cutting open the immature poppy pod, has been used to relieve pain. The Odyssey mentions the use of the analgesic drink "νεπενθε", probably opium. In the nineteenth century, the alkaloid morphine was isolated from opium (alkaloids are substances that give a basic reaction in solution), which actually has an analgesic effect. Morphine acts on opioid receptors in the central nervous system, of which there are several types, the most important being the mi, kappa, delta and the nociceptin receptor (another name is the "opioid receptor-like receptor"). Opioid receptors belong to the superfamily of G-protein-coupled receptors. Morphine binds particularly strongly to the mi-receptors, which are the most widespread and have the greatest importance for pain control. There are three subtypes of mi-receptors: mi1, whose activation produces analgesic and euphoric effects, mi2, whose activation produces respiratory depression and bradycardia, and mi3. Kappa-receptors (of which there are 4 subtypes) are predominantly located in the spinal cord; their activation produces miosis, sedation, spinal analgesia, and increased release of antidiuretic hormone from the posterior pituitary. Delta-receptors (there are 2 subtypes) are located primarily in peripheral organs, and to a lesser extent in the central nervous system (they modulate spinal analgesia). When delta-receptors are activated, in addition to the analgesic effect, a neuroprotective effect also occurs. Opioid receptors that regulate pain are located in pathways that transmit pain information (particularly in the gelatinous substance of the posterior horns of the spinal cord and along the spinothalamic tract) and in structures in the brain that process this information (limbic structures, thalamus, and hypothalamus). Activation of opioid receptors results in a decrease in the activity of these pathways and a decrease in the significance of pain in the patient's consciousness.

The term "opioids" is used to designate all substances that bind to opioid receptors and act similarly to morphine, a derivative of opium. In addition to the endogenous opioids **endorphins, enkephalins, and dynorphins** (discussed in the chapter on neurotransmission in the CNS), many exogenous substances can bind to opioid receptors, which we call exogenous opioids.

Exogenous opioids are generally well absorbed from the digestive tract, and penetrate all tissues, including the CNS. Opioids, especially morphine, should be administered with great caution to pregnant women, because the fetal liver has a very low capacity to metabolize these substances; opioids therefore tend to accumulate in fetal tissues.



Морфин

Exogenous opioids that act as agonists exhibit a number of pharmacological effects. First of all, they act analgesically (reduce the sensation of pain and the emotional reaction to it) and cause euphoria (a strong feeling of well-being). In people who receive morphine for the first time, dysphoria (action on mi receptors) may occur instead of euphoria. They reduce the respiratory rate and the sensitivity of the respiratory center in the medulla oblongata to the concentration of carbon dioxide in the blood, which

can lead to complete cessation of breathing (respiratory depression). Opioids disinhibit the parasympathetic nucleus of the oculomotor nerve (3rd cranial nerve), resulting in miosis. Through their action on the hypothalamus, these drugs increase the release of prolactin and antidiuretic hormone from the pituitary gland. In the gastrointestinal and urinary tracts, opioid agonists increase sphincter tone and reduce smooth muscle activity in the intestinal and bladder walls, respectively, resulting in constipation and urinary retention (in people who otherwise have difficulty urinating). Opioid agonists have an immunosuppressive effect (they reduce cellular immunity), and can cause the release of histamine from mast cells (sometimes a feeling of itching occurs, and in people with asthma, bronchoconstriction may occur). Finally, opioids suppress cough, i.e. they have an antitussive effect.

After prolonged use of opioids with a high affinity for mi-receptors, people become **tolerant** to their effects (this means that the dose of the substance needs to be increased to maintain the effect) and the patient develops **dependence**, which is both psychological and physical. Brain structures "adapt" to the constant presence of the drug, so that when the drug is suddenly discontinued, a disorder occurs that manifests itself in the following symptoms: dilated pupils, fever, sweating, nausea, vomiting, goosebumps, insomnia and a jump in blood pressure. We call the set of these symptoms by one name: **withdrawal syndrome**. Withdrawal syndrome begins 6-12 hours after stopping the drug, is strongest after two days and passes in less than a week.

If a person becomes tolerant to one of the opioids, he is also tolerant to the others. We call this phenomenon "cross-tolerance". However, after developing tolerance to opioids with lower intrinsic activity (efficacy), such as morphine, a person may still respond to opioids with very high intrinsic activity (e.g., fentanyl), because such drugs require a smaller absolute number of receptors to act.

If a person is addicted to opioids, they can be freed from the addiction by replacing the drug they are addicted to with an opioid that has a long half-life, i.e., long-acting, and then gradually withdrawing the other drug. This prevents the occurrence of a severe withdrawal syndrome, because the body gradually adapts to the state without the use of exogenous opioids. In order to get rid of opioid addiction, opioids with a long half-life are used: methadone or its derivative L-α-acetyl-methadol (LAAM), which has about twice the half-life of methadone.

When opioid agonists are used to treat pain, they should be dosed continuously, at fixed intervals, so as not to allow the patient to experience the full intensity of the pain again. It is a bad practice to administer opioids “on demand”, i.e. when the patient asks (or rather cries) because he can no longer bear the pain; then the patient suffers, and the doctor must administer higher doses than usual to relieve the pain.

Characteristics of certain exogenous opioids

Morphine predominantly activates mi-opioid receptors. It is used to treat moderate to severe pain, pulmonary edema (reduces dyspnea), myocardial infarction and as a premedication for major surgical interventions. It can be administered intravenously, intramuscularly, subcutaneously, epidurally or orally. When administered orally, due to rapid conjugation in the liver and the "first pass" effect, it is necessary to administer significantly higher doses, in the form of delayed-release tablets or capsules..

Recently, the use of morphine by the method of “patient-controlled analgesia” has been very popular. Morphine is administered parenterally, through an indwelling catheter, and with the help of a computer-controlled pump. By pressing a button, the patient can inject himself with morphine, whenever he wants, but only up to the maximum allowed by the computer program. This allows for better pain control, with a lower total dose of morphine.

Morphine and other opioids are contraindicated in patients with brain injury, because they increase intracranial pressure due to vasodilation. Morphine should also be avoided during labor, because it prolongs labor and causes respiratory depression in the newborn. Alcohol, sedatives, neuroleptics, and other sedative drugs should be avoided during morphine use, because they potentiate the respiratory depression. Concomitant use of corticosteroids should also be avoided, because they potentiate the immunosuppressive effect.

Codeine is also a natural alkaloid, which, together with morphine, is found in the pods of the opium poppy. It is much weaker than morphine, so it is used to treat mild to moderate pain, and as an antitussive. It is often used in combination with non-opiate analgesics. Some of the codeine ingested is metabolized to morphine. Since codeine rarely causes euphoria, it is not abused.

Hydrocodone, oxycodone, dihydrocodeine and oxymorphone are derivatives of codeine or morphine that are used in combination with non-opioid analgesics to treat mild to moderate pain. Oxycodone is interesting because it does not have a pronounced antitussive effect, so it can be used as an analgesic in pulmonary patients who need to maintain the ability to cough.

Meperidine (synonyms: pethidine, petantine) in addition to its analgesic effect also has a strong anticholinergic effect. Compared to morphine, it has a five-fold lower potency, which begins more quickly and lasts for a shorter time (2 hours) than morphine. The metabolite of meperidine, normeperidine, has excitatory effects, causing mild agitation instead of sedation, and if overdosed, convulsions or hallucinations occur. It should not be given together with MAO inhibitors, because convulsions are more frequent. Meperidine is often used for analgesia during childbirth because it has a shorter duration of action and is eliminated more quickly from the newborn's body than morphine; in addition, it increases uterine contractions. Meperidine is also useful as an analgesic in pulmonary patients, because it suppresses cough less than morphine.

Diphenoxylate, its metabolite difenoxin, and loperamide are derivatives of meperidine used as antidiarrheals.

Fentanyl is an opioid analgesic about 100 times more potent than morphine. It is primarily used as an adjunct to general anesthesia. As an analgesic for chronic pain, it is administered in the form of a transdermal patch, because it is easily absorbed through the skin due to its high liposolubility. The patch is applied to the skin and changed every 3 days. Fentanyl and similar drugs (sufentanil, alfentanil) are contraindicated in pregnancy because they are teratogenic. They should also never be given during or immediately before labor because they cause severe respiratory depression in the mother and newborn; sudden infant death syndrome has been described after the use of fentanyl.

Fentanyl, sufentanil, and alfentanil also have significant effects on the cardiovascular system and should be used with caution in patients with cardiovascular disease. They cause bradycardia and hypotension due to vasodilation. **Levorphanol** is the l-isomer of a morphine derivative that is five times more potent than morphine. It is similar in appearance to morphine and is used instead in some countries.

Methadone has a longer duration of action than morphine (~12 hours for methadone, and ~4 hours for morphine) and accumulates in the body (in fatty tissue). Due to this, the cessation of methadone is accompanied by a milder withdrawal syndrome than the cessation of morphine. Methadone is currently most commonly used to alleviate withdrawal syndrome in morphine addicts. It has also been shown that it is beneficial to replace heroin with methadone in pregnant women, as the consequences for the future cognitive development of the child are less. Methadone prolongs the QT interval in the ECG, i.e. it can lead to ventricular arrhythmias, so it is necessary to frequently monitor the ECG when introducing this drug. Several semi-synthetic opioids have been increasingly used for oral pain therapy in the last decade: **oxycodone, hydromorphone and hydrocodone**. These drugs are full agonists of opioid receptors, which are metabolized in the liver to active metabolites. Their action lasts for a short time, up to 6 hours at most. The effect and side effects are similar to those of classical opioids, morphine, fentanyl and methadone.

Tapentadol stands out by its mechanism of action, an opioid that is a full agonist of the receptors, but also blocks the **reuptake of noradrenaline**. It is administered orally, and in terms of the strength of its analgesic effect, it is not inferior to morphine. Side effects are similar to the side effects of morphine.

In order to overcome the disadvantages of mi-agonists, so-called partial agonists have been synthesized, i.e. drugs that bind to, but very weakly activate mi-receptors, while at the same time showing high affinity for kappa-receptors and strongly activate them. Compared to morphine and similar opioids, partial agonists differ in that they cause weak physical dependence, activate the sympathetic nervous system (hence cardiac stimulation), and cause **excitation and hallucinations** in patients. This group of drugs includes **pentazocine, butorphanol, nalbuphine, buprenorphine, and dezocine**. When given together with morphine or another strong mi-agonist, partial agonists block their effects, and when given alone, they exhibit strong κ- and weak μ-effects.

Pentazocine causes respiratory depression like morphine, but is much less likely to cause constipation. It is used to relieve moderate pain, and as a premedication for general anesthesia. Specific side effects of pentazocine are sedation, psychotomimetic effects (hallucinations, nightmares, anxiety) and cardiac stimulation due to activation of the sympathetic nervous system. Therefore, pentazocine is contraindicated in patients with psychosis, epilepsy, head injuries and myocardial infarction.

Butorphanol is a stronger μ-receptor antagonist and a stronger κ-receptor agonist than pentazocine. It is used to relieve moderate to severe pain. It has very similar side effects to pentazocine. It is administered parenterally or as a nasal spray.

Tramadol is an opioid analgesic that also has **antidepressant** properties. Tramadol is a racemate, and both isomers, as well as the active metabolite, weakly activate mi-opioid receptors. One of the isomers blocks the reuptake of noradrenaline into nerve endings, and the other blocks the reuptake of serotonin. The drug is used for mild to moderate pain, and the main side effect is a confusional state, which sometimes occurs. Tramadol is less effective in about 15% of people who have a genetically determined lower activity of cytochrome 2D6, so the active metabolite of tramadol is produced less. **Tapentadol** is a newer drug that moderately activates mi-opioid receptors and blocks only the reuptake of noradrenaline. It has proven to be very effective in the treatment of postoperative pain. It does not cause a confusional state and is effective in all patients. Both drugs are administered orally.

There are also drugs that only block the action of mi-agonists: **naloxone, naltrexone, and nalmefene**. They bind to mi-receptors, but do not activate them. They are called opioid antagonists. Naloxone is used to treat poisoning with morphine and other opioids. It can awaken the poisoned patient from a coma and restore spontaneous breathing. If used in patients who are

addicted to mi-agonists, it can provoke the appearance of a withdrawal syndrome. Naloxone is given only intravenously; due to rapid glucuronidation in the liver and elimination via the kidneys, naloxone has a short half-life of only 1 hour, so it must be given repeatedly to poisoned opioids. Naltrexone is administered orally, and after absorption it is intensively metabolized in the liver. However, its main metabolite 6-beta-naltrexol is active, so the effect of naltrexone lasts for 2-3 days. Naltrexone is used to maintain abstinence in heroin addicts: they receive it continuously, so that if they reach for heroin, naltrexone will not allow them to experience euphoria. Naltrexone can also help maintain abstinence in alcohol addiction. Unlike naloxone, which has almost no side effects, **naltrexone** is hepatotoxic, causing headache, insomnia, increased blood pressure, increased appetite, blurred vision and delayed ejaculation.

Nalmefene is administered only parenterally. Due to slow metabolism in the liver by glucuronidation, nalmefene has a long half-life, about 11 hours. It is used to relieve respiratory depression in the postoperative period.

Opioids used primarily as antitussives are **dextromethorphan, noscapine, and levopropoxyphene**. Dextromethorphan is the d-isomer of levorphanol. It does not have the central effects of levorphanol, but acts only on the cough center in the medulla oblongata and depresses it. It should not be given together with MAO inhibitors, as it potentiates their side effects: hypertension and coma. Noscapine and levopropoxyphene have similar characteristics.

Table 6. Doses of the most commonly used opioids (calculated for an adult weighing approximately 70kg)

OPIOID	ROUTE OF ADMINISTRATION	SINGLE DOSE	DOSE INTERVAL
Morphine	Parenteral and oral	10 mg	6 h
Methadon	Oral	5 mg	12 h
Meperidine	Intramuscular	50 mg	6 h
Butorfanol	Intramuscular	2 mg	4-6 h
Naloxon	Intravenous	0.4 mg	*

* It is given in case of poisoning with morphine or other mi-agonists. The dose can be repeated after a few minutes if the patient does not wake up from the coma (up to a maximum dose of 10 mg). Its effect lasts for a short time (1-2 hours), so it should be administered again after 1-2 hours..

ADDICTIVE MEDICINES

Drugs that affect human mental functions have always been the subject of abuse. In the desire to replace the often sad reality with illusions, at least temporarily, people have resorted to psychoactive substances. Unfortunately, repeated use of these substances always leads to addiction in the user: the central nervous system adapts to the presence of a foreign substance (e.g., by reducing the number of receptors) so that abrupt cessation of use causes a desire to use the substance again (psychic dependence) and in some cases unpleasant physical manifestations (physical dependence). The set of symptoms that occurs after stopping taking the substance to which the user is addicted is called **abstinence syndrome**. According to the classification of the World Health Organization, there are several types of addiction.

Alcohol-barbiturate type of addiction. The main psychological effects of alcohol, barbiturates, benzodiazepines and other sedatives are short-term euphoria (a state of pleasure, well-being and sometimes excitement reminiscent of orgasm), calming and relieving anxiety. Attention weakens, the thought process is significantly impaired and social considerations in behavior are lost. With increasing doses, loss of coordination of movements, drowsiness and coma follow. Of the barbiturates, the most abused are those with short action: pentobarbital, amobarbital and secobarbital. The most commonly abused benzodiazepines are diazepam, lorazepam, flurazepam and midazolam.

Tolerance to these substances develops over time, so it is necessary to take progressively higher doses to achieve the same effect. Both physical and psychological dependence develop, and the withdrawal syndrome is particularly severe (delirium, anxiety, sweating, hallucinations, muscle cramps, tremors and convulsions in about 2% of addicts). The withdrawal syndrome is treated by re-administration of substances from this group, followed by a gradual reduction in their dose. The most commonly used benzodiazepines are those that are slowly metabolized (diazepam or chlordiazepoxide), because their blood concentration gradually decreases when administration is discontinued, which gives the CNS time to adapt to the new environment. For example, diazepam is first administered at 40 mg per day for 4 days, then 30 mg per day for 3 days, then 20 mg per day for 2 days and finally 10 mg only one day before complete cessation of administration..

ETHANOL

Ethanol is a simple alcohol, with only two methyl and one hydroxyl group (CH3CH2OH). After oral administration, it is well absorbed from all segments of the gastrointestinal tract (as much as 20% of the ingested amount is absorbed from the stomach); the intake of fatty foods before or during alcohol consumption slows down absorption. After absorption, it is distributed in both the extracellular and intracellular space. In pregnant women, it easily passes through the placental barrier. Ethanol is metabolized in the liver under the action of two enzymes: the largest part (90%) is broken down by alcohol dehydrogenase from the cytoplasm, and a smaller part by microsomal oxidase P450 2EI. Both enzymes transform ethanol into acetaldehyde, which is further converted into acetic acid under the action of the aldehyde dehydrogenase enzyme from the cytoplasm.

Ethanol metabolism is a capacity-limited process, so that a maximum of 10-15 ml of pure ethanol can be broken down in 1 hour. Such elimination kinetics, when the same amount of substance is always eliminated per unit of time, are called zero-order kinetics. Over 90% of ingested ethanol is eliminated by degradation in the liver to acetic acid; the remaining 5-10% is eliminated in the urine and in exhaled air.

Some drugs can inhibit the enzyme aldehyde dehydrogenase, and thus lead to the accumulation of acetaldehyde after ethanol intake. Acetaldehyde is a toxic substance that causes vasodilation, hypotension, facial flushing, headache, nausea and vomiting, chest pain, and difficulty breathing. One drug with such an effect, disulfiram, is used in alcohol withdrawal therapy, because it prevents the person taking it from drinking alcohol. Other drugs that inhibit aldehyde dehydrogenase are: metronidazole, some third-generation cephalosporins, griseofulvin, oral antidiabetics from the sulfonylurea group, and phenothiazines. The mechanism of action of ethanol involves increasing the activity of receptors for the inhibitory neurotransmitter GABA, and decreasing the activity of receptors for the excitatory neurotransmitter glutamate. Thus, ethanol actually has a depressant effect on the central nervous system. At the beginning of the effects of ethanol, due to the depression of the inhibitory functions of the brain, the person experiences euphoria, becomes aggressive, and loses control over his behavior (the popular name for this stage is the "monkey stage"). Then comes difficulty speaking, ataxia, slowed thinking and reflexes ("bear stage"), and finally the person falls asleep and falls into a coma, with loss of control over the sphincters (popularly mockingly "pig stage"). When the patient sobers up, i.e., the ethanol is metabolized, the patient experiences a hangover, an unpleasant state with headache, sweating, tremors and nausea.

Ethanol affects other organs in addition to the central nervous system. It causes vasodilation, especially in the skin, so that people intoxicated with ethanol cannot conserve body heat, but become hypothermic, i.e., their temperature equalizes with the ambient temperature. Due to the inhibition of vasopressin secretion in the neurohypophysis, ethanol has a diuretic effect, i.e., it increases the excretion of dilute urine. In the stomach, ethanol increases acid secretion and leads to atrophy of the mucous membrane; in the small intestine, it damages the luminal membrane of enterocytes and interferes with the absorption of amino acids and vitamins.

After chronic consumption of large amounts of alcohol (in alcoholics), damage occurs to a whole range of organs. Cirrhosis develops in the liver, and myopathy in the heart. Attacks of acute pancreatitis are frequent, peripheral nerves are damaged (neuropathy) and the gonads atrophy, with a decrease in the secretion of sex hormones (in both women and men). Wernicke's encephalopathy (paralysis of the cranial nerves) and Korsakoff's psychosis develop in the brain (the alcoholic compensates for gaps in memory with fabrications).

If the mother drinks alcohol during pregnancy (more than 90 ml per day), during the period of organogenesis, the child develops a defect called "fetal alcohol syndrome". This syndrome consists of: small head, short stature, short slits between the eyelids, lack of a philtrum, thin upper lip, micrognathia, short, snub nose with a sunken nasal bridge, motor disorders, and anomalies of the heart, external genitalia, and inner ear.

In acute alcohol poisoning, the patient is usually in a coma when he reaches a doctor. It is then essential to secure the airway and ventilate the patient if breathing stops. Intravenous administration of glucose (always with concomitant administration of vitamin B1) may be useful. In the most severe cases of ethanol poisoning, it can be eliminated by hemodialysis.

A new drug for maintaining abstinence from alcohol is called acamprosate. This drug is chemically similar to gamma-aminobutyric acid, and therefore activates GABA receptors and antagonizes the effects of glutamate. The consequence of this effect of acamprosate is a reduced desire to drink alcohol. Among the side effects, acamprosate can cause abdominal pain, rash with itching, decreased libido and frigidity, or impotence..

Opioid type of addiction. Of the opioids, the most abused is the morphine derivative, heroin (diacetylmorphine), which, due to its high liposolubility, reaches the brain the fastest and therefore has the fastest effect. Heroin is most often administered intravenously, but it can also be smoked or snorted. In a person using heroin for the first time, malaise, nausea, and vomiting usually occur. In experienced users, heroin and other opioids lead to euphoria and a feeling of a hot wave passing through the extremities (similar to that of orgasm). These feelings last for a few minutes, followed by sedation and relaxation, lasting about an hour.

Opioid use is accompanied by tolerance, psychological, and physical dependence. Unfortunately, tolerance is weak to the depressive effect on breathing, and not at all to miosis and constipation. Withdrawal syndrome (dysphoria, anxiety, sweating, cold and clammy skin ["cold turkey"], rhinorrhea, vomiting, diarrhea, fever, muscle pain) is treated with methadone administration, followed by its gradual withdrawal (20 mg daily for the first three days and then 10 mg for the next three days).

Cocaine-amphetamine type. Both cocaine and amphetamine increase the amount of free catecholamines in the brain; cocaine blocks their uptake into nerve endings, while amphetamine releases them from nerve endings. Cocaine is administered by snorting, and amphetamine is administered orally. If cocaine and the amphetamine derivative, methamphetamine, are converted from salt to base, they can also be administered by smoking. Cocaine and methamphetamine can also be administered intravenously.

Both cocaine and amphetamine cause euphoria, an orgasm-like sensation, rapid thinking, excitement, anorexia, and increased alertness. These substances are most often used for periods of 1-3 days, when they are continuously administered in increasing doses; such a one-day period is called a "rush", and ends with a "crash", i.e., physical exhaustion and sleep, which lasts 1-2 days. At higher doses, stereotyped movements (grinding teeth, constantly touching the face or similar) and paranoia occur. Outside the central nervous system, stimulants cause tachycardia, arrhythmias, hyperthermia, mydriasis and an increase in blood pressure.

Their abuse is accompanied by psychological and weak physical dependence. Tolerance develops quickly, which is why during the "rush" the doses are increased. The withdrawal syndrome is weakly expressed (dysphoria, increased appetite, drowsiness) and does not require special therapy.

Long-term use of substances from this group leads to permanent damage to neurons, and the appearance of psychosis very similar to schizophrenia.

Hallucinogenic type of addiction. The term "hallucinogen" is used to refer to substances that disrupt perception, primarily visual and auditory. However, in addition to perception, hallucinogens also affect the thought process and mood. Therefore, in addition to the term "hallucinogens", the terms "psychedelic" and "psychotomimetic" (imitate psychosis) are also used. This group of substances can be divided into two subgroups: ***phenylethylamine derivatives*** (mescaline, methylenedioxyamphetamine [MDA], methylenedioxymethamphetamine [MDMA] and dimethoxymethylamphetamine [DOM]) and ***indoleamine derivatives*** (psilocybin, N,N-dimethyltryptamine [DMT], lysergic acid diethylamide [LSD]). Phencyclidine (PCP), an analogue of ***piperidine***, differs in its chemical structure from the aforementioned groups, but also has a hallucinogenic effect. All hallucinogens have a high affinity for serotonin $5HT_2$ receptors, on which they act agonistically.

The natural alkaloids mescaline (from the Mexican prickly pear cactus, peyote, Lophophora Williamsii) and psilocybin (from South American mushrooms, from which the ingestion preparation, ayahuasca, was made) have been used for centuries by Indians to establish contact with the spirits of their ancestors, i.e., to delve into their own subconscious. Synthetic substances, primarily LSD, have been used by many artists as an aid to better understanding their own being and the world. Today, the use of these substances is prohibited by law in most countries.

LSD is taken orally, and causes effects that last up to 8 hours. The state in which a person was before taking LSD greatly depends on what the effects will be. A person who was relaxed, without fear, experiences euphoria, depersonalization, sees objects around him differently (from multiple angles, with a clear texture, with stronger colors), loses the sense of time and sometimes has hallucinations of brightly colored geometric images. On the other hand, a person who was tense and scared may become even more anxious, may experience a panic attack and get paranoid ideas.

MDMA is also known as "ecstasy". This substance has both a hallucinogenic and stimulant effect. Initially, euphoria occurs, and the person who has taken ecstasy becomes more self-confident, and communicates with others more easily. Higher doses cause hallucinations and stimulation of the cardiovascular system (tachycardia, hypertension, arrhythmias). Similar effects are produced by MDA, which also creates a feeling of closeness with others, and is popularly called the "love substance".

Phencyclidine ("angel dust") has both a stimulant and a hallucinogenic effect. A person under its influence feels happy, and believes that they are working and thinking quickly and efficiently. Auditory hallucinations are particularly common. In higher doses, it acts as an anesthetic (similar to ketamine), causing incoordination, catalepsy, amnesia, and then coma.

Hallucinogens are characterized by a pronounced tolerance, which is cross-reactive (e.g., if someone becomes tolerant to psilocybin, they are also tolerant to LSD and other hallucinogens). Hallucinogen addiction is only psychological in nature; there is no withdrawal syndrome.

Cannabis is a type of addiction. The Indian hemp plant, whose Latin name is Cannabis sativa, (marijuana and hashish are preparations made from it: marijuana is a dried and chopped plant, and hashish is the resin from its buds), contains tetrahydrocannabinol, which causes euphoria accompanied by drowsiness, hallucinations, impaired perception of time, relaxation and weakening of immediate memory. The effects occur quickly, reaching a maximum after 30 minutes, and last for 4-6 hours. Tetrahydrocannabinol acts through its receptors, which are designated CB1, and which are found in high concentrations in the cerebellum, extrapyramidal structures, hippocampus and cortex. In addition to the above effects, tetrahydrocannabinol has an analgesic effect, increases appetite, causes tachycardia, pronounced conjunctival hyperemia ("bloodshot eyes"), bronchodilation and a decrease in intraocular pressure.

There is only psychological dependence. Sometimes inexperienced people who use marijuana or hashish experience a panic reaction and fear. There is no hangover after using marijuana.

Addiction to organic solvents. Most organic solvents (volatile hydrocarbons), which are found in various glues, paints, hairsprays, etc., can be enjoyed if inhaled in a closed space (e.g. from a plastic bag). They cause euphoria and hallucinations in the user. If overdosed, they lead to depression of the central nervous system. They cause tolerance, psychological and physical dependence. Withdrawal syndrome does not always occur, but when it does, it resembles alcohol withdrawal syndrome.

Organic solvents that are inhaled have carcinogenic, cardiotoxic, neurotoxic, and hepatotoxic effects.

Nicotine addiction. Nicotine from cigarettes causes mild euphoria, increased alertness, and reduces irritability. Nicotine causes both physical and psychological addiction, which are extremely persistent. The withdrawal syndrome after quitting smoking, which consists of irritability, loss of concentration, increased appetite, and constipation, lasts for several months. By using small doses of nicotine released from special chewing gums, the withdrawal syndrome can be overcome more easily.

The drug bupropion, which acts as a selective inhibitor of the reuptake of noradrenaline and dopamine into nerve endings, can be useful in nicotine withdrawal. Bupropion must be dosed carefully, because in higher doses it can cause epileptic seizures or acute psychosis.

Pregabalin addiction. Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA), but it does not bind to its receptors. Pregabalin modulates the release of other neurotransmitters in the central nervous system. As a drug, it is used for neuropathic pain, epilepsy, and generalized anxiety disorder. Because it causes euphoria, it has a high potential to cause addiction, which is both psychological and physical. A person under the influence of large doses of pregabalin is hyperactive, but at the same time clumsy due to poor coordination of movements and tremors, so injuries are possible. Insatiable hunger occurs, so the addict uncontrollably eats all the food that comes to hand. Tolerance is created to the euphoric effect, so the addict progressively takes higher and higher doses. When pregabalin is abruptly stopped, the withdrawal syndrome is relatively mild: headache, anxiety, sweating, diarrhea. A major problem in practice is the fact that most doctors and pharmacists are unaware of the potential of pregabalin to cause addiction, so they prescribe and dispense it without sufficient control, thereby encouraging the onset of addiction**.**

NON-STEROID ANTIINFLAMMATORY DRUGS

In addition to glucocorticoids, steroid hormones that, among other things, have anti-inflammatory effects, there are substances with a different chemical structure and similar anti-inflammatory effects. They are called "non-steroidal anti-inflammatory drugs" and can be divided into drugs that inhibit cyclooxygenase and drugs that act by other mechanisms (other non-steroidal anti-inflammatory drugs).

Cyclooxygenase inhibitors

Cyclooxygenase inhibitors prevent the formation of prostaglandins, thromboxanes and prostacyclins. Since all these substances are mediators in the inflammatory process, the use of inhibitors leads to the calming and withdrawal of all signs of inflammation. Cyclooxygenase inhibitors are used to treat acute and chronic inflammations whose cause is not infectious in nature (rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, bursitis, etc.). Unfortunately, these drugs act only symptomatically; they have no effect on the progression of the disease itself. In addition to the anti-inflammatory effect, all drugs from this group have analgesic and antipyretic effects. The antipyretic effect can be explained by the blockade of the

formation of prostaglandin E (PgE) in the choroid plexus of the cerebral ventricles under the influence of interleukin 1 from leukocytes; PgE otherwise causes an increase in body temperature by adjusting the thermoregulatory center in the hypothalamus to a higher temperature.

Cyclooxygenase

The enzyme cyclooxygenase exists in two forms: cyclooxygenase 1 (COX 1) and cyclooxygenase 2 (COX 2). COX 1 is found in all tissues and its activity changes very little during the life of an individual. COX 2 is found primarily in cells involved in inflammatory processes (leukocytes, macrophages, etc.) and its activity increases significantly during inflammation. It is believed that inhibition of COX 2 achieves therapeutic effects in inflammation, while inhibition of COX 1 results in adverse effects. COX 1 is selectively inhibited by indomethacin, both COX 1 and COX 2 are inhibited by ibuprofen, and COX 2 is selectively inhibited by celecoxib, rofecoxib, etoricoxib and nabumetone.

The first representative of this group of drugs is acetylsalicylic acid, known by the popular trade name aspirin. Aspirin is well absorbed from the digestive tract, and quickly after absorption is broken down by non-specific esterases in the gastrointestinal tract and liver to acetate and salicylic acid. Salicylic acid is highly bound to plasma proteins and metabolized in the liver by conjugation with glucuronic acid or glycine (the main metabolic pathway) and oxidation to gentisic acid (a minor metabolic pathway). Salicylic acid penetrates all tissues by diffusion. Metabolites are excreted in the urine; the rate of excretion depends on the pH of the urine - the higher the pH, the faster the drug is excreted. At high doses of aspirin, the metabolic pathways in the liver become saturated; thus, the linear elimination kinetics transition to saturation kinetics, and finally to zero-order kinetics. Thus, the half-life of salicylic acid is 3-6 hours when using low doses of acetylsalicylic acid, and as much as 15-30 hours when using high doses.

- Acetylsalicylic acid irreversibly inhibits COX 1 and COX 2, while salicylic acid inhibits the same enzymes reversibly. Aspirin is used to treat mild to moderate pain, to reduce elevated body temperature, as an anti-inflammatory agent in some rheumatic diseases and, in small doses, as an antiplatelet agent.
- If extremely high doses of aspirin are used (more than 4-5 g per day), the drug accumulates in the tissues and poisoning occurs. Initially, tinnitus and hyperventilation occur, and then, due to the disruption of oxidative processes in the cells, carbon dioxide accumulation, acidosis and respiratory depression occur. The elimination of aspirin and its metabolites can be accelerated by increasing diuresis and alkalinizing the urine (forced alkaline diuresis).
- Since prostaglandins (the synthesis of which is reduced by these drugs) are necessary for the normal functioning of all tissues, the side effects of aspirin (and other cyclooxygenase inhibitors) are numerous:
    - erosive gastritis with bleeding through the stool (due to the blockade of the synthesis of prostaglandin E1, which maintains good blood flow through the mucosa);
    - low doses of aspirin worsen gout, because they make it difficult for the kidneys to excrete uric acid. Large doses paradoxically increase the excretion of uric acid;
    - deterioration of kidney function (because prostaglandins are necessary for the regulation of blood flow in the renal cortex), accompanied by fluid retention;
    - high doses of all nonsteroidal anti-inflammatory drugs, both selective and nonselective, lead to hypertension, worsening of heart failure and atherothrombotic events such as myocardial infarction or stroke;
    - in young children, aspirin can cause Reye's syndrome (encephalopathy and liver failure) if administered during a viral infection (influenza, chickenpox). Therefore, the use of aspirin in children under 8 years of age, and in older children with viral infections, is contraindicated;
    - worsening of asthma (because the blockade of prostaglandin synthesis increases the synthesis of leukotrienes, the main bronchoconstrictors in asthma);
    - if these drugs are administered to pregnant women in the last trimester of pregnancy, they can delay the onset of labor and increase the risk of stillbirth; Children who are born have low birth weight and a higher risk of intracranial hemorrhage.

Salicylates (acetylsalicylic acid and salicylic acid) interact with other drugs in a serious way, which has significant consequences. First of all, salicylates displace anticoagulants and sulfonylurea derivatives from plasma proteins; thereby increasing the free fraction of these drugs in plasma, and leading to an increase in their effect, i.e. bleeding, or hypoglycemia. Salicylates also enhance the effect of insulin, and reduce the effect of loop diuretics. Patients should be warned not to take alcohol with aspirin, as this increases the risk of developing acute gastric ulcers.

In addition to aspirin, this group of drugs includes acetic acid derivatives (indomethacin, diclofenac, ketorolac, tolmetin), propionic acid derivatives (ibuprofen, flurbiprofen, ketoprofen, naproxen), oxicams (piroxicam), phenamates (meclofenamate, mefenamic acid), pyrazolones (phenylbutazone and oxyfembutazone) and others (sulindac, ketorolac, etc.). In terms of efficacy and side effects, these drugs differ to some extent from aspirin.

Acetic acid derivatives constitute a relatively heterogeneous group in pharmacodynamic terms. Indomethacin is the most potent cyclooxygenase inhibitor, but due to its pronounced toxicity (severe headache, gastrointestinal bleeding, bone marrow damage, vasoconstriction of coronary arteries, blurred vision, corneal deposits) it is used only when other drugs from this group are ineffective: in severe rheumatic diseases and acute gout attacks. It is also used in premature infants to induce closure of the ductus arteriosus "Botalli". Indomethacin is contraindicated in pregnancy, in asthmatics and in people with depression (because it can worsen it, by a currently unknown mechanism). In terms of function, sulindac and etodolac are very similar to indomethacin. Sulindac is a prodrug, which is metabolized to the active sulfide metabolite; less damaging to the gastric mucosa than indomethacin, because when ingested, as a prodrug, it does not inhibit prostaglandin synthesis in the mucosa.

Diclofenac is administered orally, rectally, and parenterally, and is very effective; its use is currently limited due to pronounced cardiovascular toxicity (hypertension, worsening of heart failure, myocardial infarction). Ketorolac is notable for its potent analgesic activity (which may involve the release of endogenous opioids), which is why it is used to treat postoperative pain.

Propionic acid derivatives have a greater potency than aspirin, with a lower incidence of side effects. This group of drugs includes ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and naproxen. The main difference between the drugs in this group lies in the duration of the effect: naproxen has a long half-life, and ketoprofen, fenoprofen, and ibuprofen have a short half-life.

The fenamates (meclofenamate and mefenamic acid) are effective cyclooxygenase inhibitors, but in children they cause more side effects than other cyclooxygenase inhibitors. Also, if these drugs are overdosed, they can provoke convulsions. Therefore, they are used only in patients who are resistant to the effects of other drugs from the group of nonsteroidal anti-inflammatory drugs.

Pyrazolones (phenylbutazone and its active metabolite oxyphenbutazone) are very effective anti-inflammatory drugs, but they often cause serious adverse reactions (anemia, renal failure, liver damage). Therefore, they are reserved only for the most severe pain, when other cyclooxygenase inhibitors have no effect. Oxicams (piroxicam) are characterized by long-term retention in the human body, which allows for one-day administration.

In recent years, it has been recognized that all nonsteroidal anti-inflammatory drugs except aspirin increase the risk of myocardial infarction or stroke in patients with any cardiovascular disease, especially in those who have had a heart attack or who have undergone coronary artery bypass grafting. The risk of myocardial infarction or stroke increases with the dose and duration of use of these drugs. Therefore, a warning has been added to the summaries of the characteristics of all drugs in this group, and it is advised that they be used as restrictively as possible in patients with cardiovascular disease.

Table 7. Doses of the most commonly used cyclooxygenase inhibitors.

DRUG	INDICATION	SINGLE DOSE	DOSE INTERVAL
Acetylsalicylic acid	Analgesic effect	500 mg, oral	4-6h
	Antiinflammatory effect	2 g, oral	8-12h
	Antiplatelet effect	300 mg, oral	48-72h
Ibuprofen	Antiinflammatory effect	400 mg, oral	6h
Piroxicam	Antiinflammatory effect	20 mg, oral	24h

Selective cyclooxygenase 2 inhibitors include celecoxib, rofecoxib, and etoricoxib, drugs that are only used orally due to their poor solubility. Since they inhibit constitutive cyclooxygenase 1 less than nonselective cyclooxygenase inhibitors, celecoxib and rofecoxib are less likely to cause gastric ulceration and bleeding, so they are more easily tolerated by people with stomach

diseases. In terms of efficacy, they do not differ from nonselective cyclooxygenase inhibitors, except that they do not have an antiplatelet effect.

Celecoxib, rofecoxib, and etoricoxib have been widely used in recent years, which has also indicated their disadvantages. It has been observed that the risk of hypertension and myocardial infarction increases several times with the use of these drugs. Therefore, the use of celecoxib, etoricoxib, and rofecoxib should be avoided in people with cardiovascular diseases.

Nonsteroidal anti-inflammatory drugs are often combined in the same drug product with caffeine and/or lower doses of opioid analgesics, primarily codeine. It is believed that the effect of such combinations is somewhat greater than the effect of nonsteroidal anti-inflammatory drugs alone, but there is no solid evidence for this from controlled clinical studies. In some patients, caffeine and codeine exhibit characteristic side effects (addiction, i.e. constipation), which can make it difficult to treat the patient.

Other antiinflammatory drugs

This group of drugs calms signs of inflammation by mechanisms that are not fully understood. Two subgroups can be distinguished, which differ in their mechanism of action and indications. These are:

1. Drugs for rheumatoid arthritis (gold, immunosuppressants, penicillamine, levamisole, antimalarials)
2. Drugs for the treatment of gout (colchicine, allopurinol, febuxostat, probenecid and sulfinpyrazone)

1. Drugs for rheumatoid arthritis

Unlike all other anti-inflammatory drugs, members of this group slow down the progression of the pathological process and can delay the onset of complications in rheumatic diseases. Their effect does not manifest itself immediately, but only after a latency of 1 month to one year. Therefore, they are sometimes called “slow-acting antirheumatic drugs”.

Immunosuppressive drugs. Drugs that cause general immunosuppression can have a beneficial effect on rheumatic diseases. **Methotrexate** (a dihydrofolate reductase inhibitor) is most commonly used to treat seropositive rheumatoid arthritis, lupus nephritis, psoriasis, and arteritis. In the low doses used to treat these diseases, methotrexate inhibits tetrahydrofolic acid-dependent enzymes that otherwise break down adenosine. Therefore, adenosine accumulates inside and outside the cells, and through its receptors inhibits the synthesis of pro-inflammatory cytokines, tumor necrosis factor (TNF alpha) and interferon gamma.

Methotrexate is very effective, but due to its pronounced toxicity (mucosal ulcers, hepatotoxicity, pneumonitis progressing to pulmonary fibrosis, bone marrow depression, the occurrence of infections), patients should be strictly monitored and necessary measures should be taken in a timely manner to avoid or reduce toxic effects. Methotrexate is teratogenic, so it is not used during pregnancy or lactation.

In addition to methotrexate, other immunosuppressive drugs are also used: **azathioprine** (a prodrug that is converted to mercaptopurine in the body) and **cyclosporine**.

Antimalarials. Chloroquine and hydroxychloroquine (4-aminoquinolines) suppress the response of T-lymphocytes to mitogens, reduce leukocyte chemotaxis, and stabilize lysosomal membranes. They are used to treat rheumatoid arthritis, juvenile chronic arthritis, Sjögren's syndrome, and systemic lupus erythematosus.

They often cause skin rash and itching, and rarely lichenoid changes, hair loss, arrhythmias due to prolonged QT interval in the ECG, and photosensitivity. They can cause irreversible retinopathy after prolonged administration of high doses (to prevent this, hydroxychloroquine is administered in doses less than 6.5 mg/kg, and chloroquine in doses less than 4 mg/kg). Warning: they must not be used to treat psoriatic arthritis **(!)** because they can cause exfoliative dermatitis. Due to significant adverse effects on the skin, these drugs should not be given together with gold salts.

Sulfasalazine is used to treat rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, and Crohn's disease. It is a prodrug that is broken down in the large intestine by bacteria to sulfapyridine and 5-aminosalicylic acid, which have anti-inflammatory effects. Sulfasalazine increases adenosine levels and inhibits the release of tumor necrosis factor and interleukin 1.

Sulfasalazine causes gastrointestinal symptoms (in 30% of patients), skin rash, and dark skin discoloration, reduces male fertility, and may increase liver enzyme levels in the blood. Rarely, it causes bone marrow depression. It may precipitate a porphyria attack.

Since sulfasalazine is a sulfonamide, it should not be given to people who are allergic to sulfonamides or other drugs with a structure similar to sulfonamides: oral antidiabetics - sulfonylurea derivatives, thiazide diuretics, furosemide.

Gold. Gold preparations (chrysotherapy) can be administered parenterally (aurothioglucose and gold sodium thiomalate) and orally (auranofin). Gold accumulates in the synovial membranes, lymphatic vessels, spleen, liver and kidney, weakens the functioning of macrophages and at that stage interrupts the chain of inflammatory reactions. It is used to treat rheumatoid arthritis

and juvenile rheumatoid arthritis, but only after other drugs that affect the course of the disease have proven ineffective. Gold preparations will lead to some improvement in 80% of patients, and to complete remission in only 20%. Oral gold preparations are less effective than parenteral ones.

Gold has numerous side effects, the most common of which are dermatitis accompanied by itching, blue or gray discoloration of the skin, photosensitization, hematotoxicity (eosinophilia, rarely cytopenias), nephrotoxicity and stomatitis. Oral gold preparations cause diarrhea. Less common are liver damage, peripheral nerve damage, deposition of gold in the cornea and so-called nitritoid reactions.

Gold preparations are contraindicated in patients with systemic lupus erythematosus, during pregnancy and lactation.

Penicillamine. Penicillamine is an analogue of the amino acid cysteine. It binds to receptors on the lymphocyte membrane and in an unknown way prevents the development of the inflammatory process. It also inhibits the formation of new blood vessels (angiogenesis). Due to its high toxicity, it is used to treat only patients with rheumatoid arthritis who have not responded to gold therapy.

Penicillamine most often causes proteinuria (in 20% of patients), hematotoxicity and dermatitis. It can provoke the appearance of many autoimmune diseases**.**

Glucocorticoids. Glucocorticoids have an anti-inflammatory effect due to the inhibition of phospholipase A2, which prevents the synthesis of prostaglandins, leukotrienes and other inflammatory mediators. They do not slow down the progression of the pathological process, but only act symptomatically.

They are used if there are extra-articular manifestations of the disease (pericarditis, iridocyclitis) of rheumatoid arthritis and for local intra-articular therapy.

Leflunomide. This is a relatively newer drug (it entered therapy only in 1998), which begins to act faster than other drugs that modify the course of the disease (in just 4 weeks). It is a prodrug that is converted into the active form in the body by cytochrome P450 oxidase, which inhibits T-lymphocyte proliferation by inhibiting the synthesis of pyrimidine bases. The active form of the drug remains in the body for a very long time, up to two years.

30% of patients taking leflunomide experience diarrhea, and 10% have nausea and vomiting. It causes a skin rash accompanied by itching, alopecia, and increased levels of liver enzymes in the serum.

Leflunomide is a teratogen. It also inhibits cytochrome CYP 2C9, so it interacts with drugs that are metabolized by this enzyme (rifampicin and others).

Levamisole. Levamisole is an immunostimulant (increases chemotaxis and phagocytosis of macrophages and polymorphonuclear cells) that paradoxically has a beneficial effect on rheumatoid arthritis. Its place in therapy has not yet been established. It has side effects similar to penicillamine**.**

Tofacitinib, baricitinib, and upadacitinib are new drugs that inhibit Janus kinases involved in joint inflammation. They are used to treat moderate to severe rheumatoid arthritis that has not responded to methotrexate therapy. Tofacitinib, baricitinib, and upadacitinib are administered orally, in two daily doses. Previous studies have shown that they can be used alone or in combination with methotrexate. The main side effects are increased infections.

Biological drugs for rheumatoid arthritis are proteins that are obtained from living cells, i.e., cytokines or their blockers. They are used to treat moderate to severe rheumatoid arthritis that no longer responds to the previously mentioned drugs. They are administered alone or in combination with methotrexate. **Etarnecept, infliximab, adalimumab, golimumab and certolizumab** block the action of tumor necrosis factor, **tocilizumab** blocks interleukin 6, **abatacept** prevents the activation of T-lymphocytes, **rituximab** binds to CD-20 B-lymphocytes and prevents their activation, and **anakinra** blocks interleukin 1. Infliximab, tocilizumab and rituximab are administered intravenously, abatacept is administered intravenously or subcutaneously, while other biological drugs are administered subcutaneously. Drugs that block tumor necrosis factor can lead to the development of bacterial, fungal and viral infections, as well as malignant tumors (lymphoma, skin cancer, etc.). Rituximab leads to progressive multifocal leukoencephalopathy and cardiac arrhythmias in a certain number of patients. Abatacept worsens chronic obstructive pulmonary disease.

Diet. Patients should be advised to consume plenty of marine fish, which contain large amounts of eicosapentaenoic acid (a 20-carbon fatty acid with 5 double bonds). This acid is incorporated into human cell membranes and gradually replaces arachidonic acid, which is a precursor to many inflammatory mediators.

Table 8. Doses of some medications for rheumatoid arthritis

DRUG	ROUTE OF ADMINISTRATION	DOSE
Auranofin	Oral	6 mg/24h
Hydroxychloroquine	Oral	200 mg/24h

2. Drugs for treating Gout

Uric acid is the end product of the metabolism of the purine bases adenine and guanine. A healthy person excretes about 700 mg of uric acid in the urine daily.

In the kidneys, uric acid is first filtered in the glomeruli, and then reabsorbed and secreted at the level of the proximal tubules. Reabsorption is carried out by active transport on the luminal membrane of the tubular cells, while secretion also takes place via active transport, but this time on the basal and lateral membranes of the tubular cell. Whether uric acid is excreted or reabsorbed depends on the balance of the reabsorption and secretion systems. The reabsorption of uric acid is blocked by probenecid, sulfinpyrazone and salicylates, while secretion is inhibited by thiazide diuretics and loop diuretics.

Gout is caused by an increased concentration of uric acid in the blood, which is deposited in the joints in the form of crystals, causing inflammation. Granulocytes phagocytose uric acid crystals, and then release lysosomal enzymes and lipids, which attract other granulocytes. In addition to the joints, uric acid crystals can be deposited in the subcutaneous tissue and cause inflammation there, which is clinically seen as the formation of nodules (tophi). Uric acid can be elevated in the blood due to increased production or decreased excretion in the kidneys.

Cyclooxygenase inhibitors (except acetylsalicylic acid, which inhibits the excretion of uric acid), colchicine, or corticosteroids are used to treat an acute attack of gout. To lower the concentration of uric acid in the blood and prevent gout attacks, drugs that reduce the production of uric acid (allopurinol) or drugs that increase its excretion ("uricosurics": probenecid and sulfinpyrazone) can be used. Drugs to prevent attacks should never be given during an acute gout attack, because they initially increase the concentration of uric acid and can worsen the patient's condition.

Colchicine is an alkaloid that has been used to treat gout in extracts of various plants since the 6th century AD. It binds to the microtubules of leukocytes, causing their depolymerization and thus hindering their movement to the site of inflammation.

Colchicine therapy is started at the first signs of an attack, and 1 milligram is given, and then about an hour later another half a milligram. Such small doses of colchicine have almost no side effects, and have been shown to be as effective as higher doses. The drug is administered orally or intravenously.

Colchicine is a toxic drug in higher doses, which, due to its excretion in the bile, primarily causes gastrointestinal complaints: nausea, vomiting, abdominal pain and severe diarrhea in most patients (80%). Rarely, it leads to alopecia, bone marrow depression and neuritis.

In patients with gout who have already developed tophi or who have had multiple attacks, ***uricosuric drugs (probenecid, sulfinpyrazone, benzbromarone)*** are used. Uricosuric drugs in therapeutic (higher) doses increase the excretion of uric acid in the urine by blocking the organic anion transport system, which reabsorbs uric acid. However, in small doses, uricosuric drugs inhibit only the tubular secretion of uric acid, and may even increase its concentration in the blood. Therefore, the most dangerous period during therapy with uricosuric drugs is the initial period, when due to the lower concentrations of these drugs in the blood, an increase in uric acid and provocation of gout attacks may occur. To prevent this, in the first week of therapy, patients should be given uricosuric drugs and small doses of colchicine.

When using uricosurics, the excretion of uric acid in the urine can increase so much that conditions are created for the formation of urinary calculi. The formation of calculi can be prevented by increasing diuresis (due to increased fluid intake) and alkalinization of the urine.

Probenecid is actively secreted in the renal tubules. Due to active secretion, probenecid interferes with the excretion of drugs that use the same transporter: penicillin, sulfonamides, indomethacin, sulfonylureas and sulfinpyrazone.

The side effects of probenecid are mild: skin rash, gastrointestinal complaints and drowsiness.

Sulfinpyrazone is chemically similar to phenylbutazone, but does not have anti-inflammatory properties. The side effects of sulfinpyrazone are manifested in the gastrointestinal tract: nausea, activation of gastric or duodenal ulcers, abdominal pain.

Benzbromarone is the most effective of all drugs in lowering blood uric acid (including allopurinol and febuxostat), which is due to its active metabolite, which is formed in the liver. Benzbromarone is a uricosuric, which blocks the URAT1 transporter for uric acid reabsorption in the proximal tubules. However, benzbromarone is not widely available, as the manufacturer prematurely withdrew it from use after several cases of fatal hepatitis. The risk of this side effect is about 1 in 17,000, so benzbromarone is still used in many countries.

Another way to prevent the accumulation of uric acid in the body is to prevent its synthesis. **Allopurinol** (an analogue of hypoxanthine) and **febuxostat** competitively inhibit the enzyme xanthine oxidase, thereby preventing the formation of uric acid. Hypoxanthine and xanthine accumulate in the body, which are much more soluble than uric acid and are therefore easily excreted from the body.

These drugs are used in patients with chronic gout who already have developed tophi, especially if their uric acid concentration is extremely high or if they have calculi in the renal pelvis and calyx. They are also useful in patients with gout who have not responded well to the use of uricosuric drugs. Allopurinol is also used preventively to lower uric acid levels in patients with malignant blood diseases (leukemia), in whom uric acid levels increase due to the breakdown of a large number of malignant cells during cytostatic therapy.

Since the use of allopurinol may initially temporarily increase the concentration of uric acid in the plasma (due to the mobilization of uric acid from the tophi), the patient must be given plenty of fluids (to increase urination) and sodium bicarbonate (to alkalize the urine). Sometimes colchicine can also be used prophylactically. Otherwise, a gout attack can be provoked.

Side effects of allopurinol include dermatitis, nausea, vomiting and, rarely, liver and bone marrow damage.

Febuxostat may cause an increase in serum transaminases. It is metabolized in the liver, and excreted equally via the kidneys and bile.

Finally, acutely elevated uric acid (e.g. in malignant blood diseases) must be rapidly reduced because it can cause acute renal failure. This can be done by intravenous administration of ***rasburicase***, a urate oxidase enzyme that converts uric acid into allantoin, a substance that is easily excreted in the urine.

PARACETAMOL

Paracetamol (synonym: acetaminophen) is an analgesic-antipyretic. It is derived from phenacetin, which was withdrawn from use due to its high nephrotoxicity. Acetaminophen has analgesic and antipyretic effects, but does not have significant anti-inflammatory and antiplatelet effects. Unlike cyclooxygenase inhibitors, it does not irritate the gastrointestinal tract. It is the antipyretic of choice (dose is 500 mg/4-6 hours orally). Its use in pregnancy is completely safe.

In recent years, paracetamol has been successfully used as a postoperative analgesic, when administered parenterally. Its advantage in this indication over nonsteroidal anti-inflammatory drugs is that it does not increase the risk of developing stress ulcers of the stomach.

In lower doses, paracetamol is well tolerated, but higher doses (greater than 4 grams per day) can lead to the accumulation of a very toxic secondary metabolite, **N-acetyl-p-benzoquinone**, which causes centrilobular necrosis of the liver. When the liver runs out of glutathione, which binds to the toxic metabolite and neutralizes it, the aforementioned centrilobular necrosis occurs. From the moment of oral ingestion of a toxic dose of paracetamol, a latent period of 12-24 hours must pass before the first symptoms of poisoning (nausea, vomiting) appear, and as many as 72 hours before signs of liver damage appear. Acetaminophen poisoning is treated with a sulfhydryl group donor, **acetylcysteine**, which binds to benzoquinone instead of glutathione and prevents its toxic effects. Acetylcysteine is administered orally.

NEFOPAM

Nefopam is a centrally acting non-opioid analgesic that inhibits the reuptake of noradrenaline, dopamine, and serotonin, and blocks NMDA receptors for glutamate. It does not cause respiratory depression, but has sympathomimetic and antimuscarinic side effects. It is administered orally (60 milligrams three times a day) or intravenously (20 milligrams per dose), which has an analgesic effect equivalent to 6-12 milligrams of morphine administered intravenously.

Nefopam is used when nonsteroidal anti-inflammatory drugs cannot control pain, and opioid analgesics are not yet necessary.

TUMOR NECROSIS FACTOR (TUMOR NECROSIS FACTOR alpha – TNF alpha) AND DRUGS THAT ACT THROUGH IT

Tumor necrosis factor is a cytokine that exists in two forms: TNFalpha or **cachectin**, produced by macrophages, and TNFbeta or **lymphotoxin**, produced by lymphocytes.

TNF is produced in the body in response to the appearance of toxic substances, e.g., bacterial toxins, but also in inflammatory diseases. Its excessive production or exogenous administration in higher doses can lead to toxic shock and cachexia.

TNFalpha itself has limited use as a drug. It is used together with some cytostatics (melphalan) for the treatment of soft tissue sarcomas of the extremities, in the form of isolated perfusion of the extremities. The total dose used ranges from 3 to 4 mg.

Locally, TNFalpha causes pain and swelling of the skin, and thrombosis, nail loss and tissue necrosis can occur. If more than 10% of the dose "leaks" into the systemic circulation, fever, nausea and vomiting, arrhythmias, liver damage and shock will occur.

Adalimumab is a human monoclonal antibody that binds to and neutralizes TNF. It is used to treat rheumatoid arthritis that is unresponsive to other disease-modifying drugs. It is administered as a subcutaneous injection, 40 mg twice a month, most often together with other rheumatoid arthritis drugs.

Side effects of adalimumab include: redness, pain and swelling at the injection site; increased incidence of serious infections and sepsis; rarely, lymphoma or demyelination.

Infliximab is a chimeric monoclonal antibody to TNFalpha, formed by fusing a human Fc fragment and a mouse Fab fragment. It is used to treat rheumatoid arthritis and Crohn's disease resistant to other therapy. It is administered as an intravenous infusion, at a dose of 3-5 mg/kg of body weight, at intervals of 2, 6 and then 8 weeks.

During the infusion of infliximab, fever, chills, chest pain, increase or decrease in blood pressure occur. Like adalimumab, it increases the frequency of serious infections (tuberculosis, etc.) and can lead to the appearance of lymphoma.

Both adalimumab and infliximab are effective only in some patients, so if positive effects are not shown within three months, further administration should be discontinued.

Etarnecept is a soluble receptor for TNF (p75). When administered, it binds to TNF and prevents its interaction with endogenous receptors. It has shown efficacy in patients with rheumatoid arthritis resistant to other therapy, as well as in juvenile idiopathic arthritis that does not respond to other therapy.

Etarnecept is administered as a subcutaneous injection (25 mg, twice a week). The half-life of etanercept is approximately 115 hours.

Adverse effects of etanercept include: local reactions (redness, pain, swelling), the occurrence of serious infections and sepsis, demyelinating diseases and aplastic anemia (rare).

Golimumab is a monoclonal antibody that binds to TNF alpha, both to the form that is already in circulation and to the form that is bound to cell membranes (transmembrane form), and leads to its inhibition. It is used to treat rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Like other drugs in this class, it reduces patients' resistance to infections.

Certolizumab is a soluble Fab fragment of a humanized antibody that binds to TNF alpha, both in the circulating form and in the form bound to cell membranes. Both its efficacy and side effects are similar to those of other drugs in this class.

ANTAGONISTS OF INTERLEUKINS

Interleukins are cytokines produced by leukocytes and other cells; they play a key role in the activation and differentiation of immune system cells, as well as in their proliferation, maturation, migration and adhesion. In other words, interleukins are involved in the body's immune reactions and the development of many autoimmune diseases.

Interleukin 1 activates lymphocytes and macrophages, and raises the hypothalamic thermostat to a higher level, i.e., leads to an increase in body temperature. Interleukin 1 blockers are **anakinra** (a recombinant form of the interleukin 1 receptor, used to treat rheumatoid arthritis), **canakinumab and rilonacept** (interleukin 1 beta blockers, used to treat periodic fever syndrome).

Interleukin 2 activates T-lymphocytes. Drugs that block the action of interleukin 2 are **basiliximab and daclizumab** (monoclonal antibodies against the S25 protein, which is a subunit of the interleukin 2 receptor). Basiliximab is used to prevent kidney transplant rejection, and daclizumab is used to treat multiple sclerosis.

Interleukin 6 induces the stimulation and differentiation of B lymphocytes, as well as the production of acute phase proteins in the liver. A monoclonal antibody against the interleukin 6 receptor (**tocilizumab**) is used as an intravenous infusion to treat rheumatoid arthritis, cytokine release syndrome, giant cell arteritis, and systemic juvenile idiopathic arthritis. The interleukin 6 receptor is also blocked by the monoclonal antibodies **satralizumab** (used to treat neuromyelitis optica) and **sarilumab** (used to treat rheumatoid arthritis).

Interleukin 12 activates T helper lymphocytes and increases the synthesis of gamma interferon. **Ustekinumab** is a monoclonal antibody that binds to the interleukin 12 receptor; it is used to treat psoriasis, Crohn's disease, and ulcerative colitis. **Briakinumab** is a monoclonal antibody against interleukins 12 and 23 that has found its place in the treatment of psoriasis, Crohn's disease, and multiple sclerosis.

Interleukin 17 leads to an increase in the secretion of other proinflammatory cytokines and chemokines from epithelial and endothelial cells. **Secukinumab, ixekizumab, and bimekizumab** are interleukin 17 antagonists that are used to treat psoriasis and ankylosing spondylitis.

Interleukin 23 stimulates T cells to produce interleukin 17. An interleukin 23 blocker is **guselkumab**, a monoclonal antibody for the treatment of psoriasis.

The biggest problem with the use of interleukin antagonists is the increased incidence of serious infections in patients who receive them. In addition, the number of neutrophils and platelets decreases.

NEUROMUSCULAR BLOCKERS

Motor nerves release the transmitter acetylcholine at their terminals. Acetylcholine binds to nicotinic N2 receptors on the membrane of striated muscle cells (N1 nicotinic receptors are found on the membranes of ganglion cells of both the sympathetic and parasympathetic nervous systems) and leads to membrane depolarization. Two molecules of acetylcholine bind to each nicotinic receptor. Ca++ channels open on the depolarized membrane and this ion enters the cytoplasm. There it binds to the troponin-tropomyosin complex, which dissociates from myosin; the interaction of actin and myosin then becomes possible, i.e., muscle cell contraction occurs. The action of acetylcholine is interrupted by acetylcholinesterase, an enzyme located in the immediate vicinity of the receptor, which breaks down acetylcholine into acetate and choline.

Neuromuscular blockers bind to nicotinic receptors, preventing the action of acetylcholine and thus temporarily paralyzing striated muscles. There are two types of blockers. ***Succinylcholine*** first activates nicotinic receptors and leads to membrane depolarization (small fasciculations can be seen on the patient), and then maintains the membrane in a depolarized state for about 10 minutes, which results in muscle paralysis. This type of neuromuscular blocker is called depolarizing. After about 10 minutes, however, partial repolarization of the muscle cells occurs, so there is a so-called "two-type blockade": part of the muscle cells is depolarized, so such a blockade cannot be suppressed by the use of acetylcholinesterase blockers, and part of the muscle cells is repolarized, so such a blockade can be suppressed by the use of acetylcholinesterase blockers.

The second type of neuromuscular blocking agent is made up of substances that bind to nicotinic receptors but do not activate them. These are the ***nondepolarizing blockers***, which are divided into two subgroups: (1) **isoquinoline derivatives** (mivacurium, atracurium, cisatracurium, doxacurium, and tubocurarine) and (2) **steroid derivatives** (pancuronium, vecuronium, rocuronium, pipecuronium). These drugs also cause muscle paralysis.

Neuromuscular blocking agents first cause paralysis of the laryngeal muscles and other muscles of the head and neck, and only then does paralysis of other muscles occur. Finally, paralysis of the diaphragm occurs. Recovery from neuromuscular paralysis is in the reverse order of that in which paralysis occurred.

All neuromuscular blockers are chemically similar to acetylcholine, meaning they have a quaternary nitrogen in their molecule. Due to the charge of the **quaternary nitrogen**, neuromuscular blockers cannot pass through body membranes by simple diffusion, so they are not absorbed from the gastrointestinal tract, do not penetrate the blood-brain barrier, and do not enter most cells. For these reasons, these drugs are administered only intravenously, and are distributed only in the extracellular space.

After intravenous injection, the fastest onset of action is for succinylcholine (after half a minute to one minute) and rocuronium (after 2 minutes), while the other neuromuscular blockers take 3 to 5 minutes to take effect. The effect of succinylcholine lasts the shortest, only 5-10 minutes, because it is quickly broken down by pseudocholinesterase in the blood. The duration of action of non-depolarizing neuromuscular blocking agents ranges from 20-30 minutes (rocuronium, mivacurium, atracurium, cisatracurium) to 60-90 minutes (pancuronium, pipecuronium, doxacurium); their action ends due to redistribution, due to which the concentration near the nicotinic receptors decreases. Only later do they spontaneously disintegrate (atracurium and cisatracurium), are broken down by pseudocholinesterase in the blood (mivacurium), are metabolized in the liver (vecuronium) or are excreted largely unchanged in the urine (rocuronium, pancuronium, doxacurium, pipecuronium). This means that in the event of an overdose, the duration of neuromuscular blockade is prolonged many times over.

> About one in 3,000 people has a hereditary deficiency of pseudocholinesterase in their blood, so they cannot break down succinylcholine and mivacurium if they are given them. In these patients, the neuromuscular paralysis caused by succinylcholine or mivacurium lasts for 2-3 hours, until these drugs are excreted in the urine.

Succinylcholine is given to patients during induction of general inhalation anesthesia to facilitate endotracheal intubation. Rocuronium can also be used for the same indication, due to its rapid onset of action. Other non-depolarizing blockers are added

during general inhalation anesthesia to ensure sufficient muscle relaxation, necessary for performing abdominal and thoracic surgeries. In addition, they are used to administer electroshocks in psychiatric institutions: then there are no muscle spasms that were once accompanied even by bone fractures! Sometimes it is necessary to use non-depolarizing neuromuscular blockers to stop convulsions in status epilepticus or tetanus, or in situations where the patient is artificially ventilated. Additional indications for the use of nondepolarizing neuromuscular blocking agents are increased intra-abdominal pressure, increased intracranial pressure, and therapeutic hypothermia after cardiac arrest.

The effect of nondepolarizing blockers lasts about 1 hour. If it is necessary to interrupt their action earlier, the acetylcholinesterase inhibitor **neostigmine** is used. Neostigmine leads to the accumulation of acetylcholine, which displaces the blockers from the receptors and interrupts muscle paralysis.

The effects of rocuronium and vecuronium can also be interrupted with a drug called **sugammadex**. This drug binds directly to rocuronium or vecuronium, thereby interrupting their action on nicotinic receptors.

The side effects of non-depolarizing neuromuscular blocking agents are not very pronounced, and are mainly due to blockade of **muscarinic receptors in the heart** (tachycardia occurs with pancuronium, rocuronium, atracurium and mivacurium) and **histamine release** from mast cells (flushing, hypotension and bronchospasm occur with atracurium and mivacurium). Succinylcholine has several side effects: postoperative pain due to the fasciculations it causes, hyperkalemia, bradycardia due to stimulation of muscarinic receptors, and very rarely malignant hyperthermia (increased body temperature, muscle rigidity, tachycardia and acidosis).

THERAPY OF MUSCLE SPASMS AND SPASTICITY

A muscle spasm is a sudden contraction of one or more muscles (which can last for a shorter or longer period), while **spasticity** is a continuous contraction of a number of muscles. Spasticity of the striated muscles occurs as part of many neurological diseases, making movement and work very difficult for patients. Spasticity is based on damage to the central motor neuron (e.g., in cerebral palsy, after a stroke, in multiple sclerosis), resulting in loss of control over spinal reflexes and reflexes involving the cranial nerves. Reflexes become hyperactive, resulting in spasticity.

Since central neuron damage cannot be treated at the moment, the only thing that can be done is to reduce reflex hyperactivity. This can be done by increasing inhibition in the CNS, i.e., by facilitating the action of inhibitory transmitters. There are drugs that act only on muscle spasms (such as **cyclobenzaprine and methocarbamol**, which are not approved for use in Serbia), and those that are active in both muscle spasms and spasticity (**benzodiazepines, baclofen, tizanidine, gabapentin**). Drugs with peripheral action, **dantrolene and botulinum toxin**, also act on both spasms and spasticity. Methocarbamol inhibits polysynaptic reflexes in the spinal cord and subcortically. It is administered orally for the treatment of painful muscle tension, usually in the lower back (so-called lumbago). Cyclobenzaprine has a similar mechanism of action to tricyclic antidepressants and blocks 5-HT2 receptors for serotonin. It is used for the short-term treatment of muscle spasms in various painful conditions**.**

Benzodiazepines facilitate the action of the most widespread inhibitory transmitter, GABA (gamma-aminobutyric acid). Diazepam therefore has a muscle relaxant effect and can be used in the treatment of spasticity. More effective than benzodiazepines is **baclofen**, a drug that directly stimulates GABA-B receptors. In addition, baclofen has an analgesic effect, because it inhibits the release of substance P. Baclofen is particularly effective when the cause of spasticity is a spinal lesion. Side effects of baclofen are confusion, hallucinations and ataxia. If its use is stopped abruptly, hyperactivity and convulsions occur. **Tizanidine** is an alpha2 receptor agonist, which increases presynaptic inhibition of motor neurons in the spinal cord by descending noradrenergic pathways. In addition to reducing spasticity, it also has an analgesic effect. It is well absorbed from the gastrointestinal tract and is metabolized during the first pass through the liver. Side effects include drowsiness, fatigue, dry mouth, and sometimes liver damage.

Gabapentin is effective in suppressing spasticity in multiple sclerosis. It is believed that it inhibits calcium ion channels in some way, thus leading to relaxation of muscle contraction. Otherwise, it is a drug characterized by complete elimination via the kidneys and a low potential for interactions with other drugs. Side effects include drowsiness, nausea, and fatigue.

In severe forms of spasticity, the peripherally acting drug **dantrolene** can also be used, which prevents the release of calcium ions from the sarcoplasmic reticulum by blocking the ryanodine calcium channels on that organelle. It effectively suppresses spasticity, but can also cause muscle weakness. Rarely, it can cause liver damage. Dantrolene can be administered both orally and parenterally; it is slowly metabolized in the liver.

If there is spasticity of only one muscle or one isolated muscle group (e.g. spastic torticollis, blepharospasm, hemifacial spasm), it can be successfully treated by injecting a small dose of botulinum toxin into the affected muscle. **Botulinum toxin** selectively enters the endings of cholinergic nerves (including motor nerves), where it prevents the release of acetylcholine. The

effect of the injection occurs after 3 days and reaches a maximum after 2 weeks; it lasts up to 12 weeks, after which the injection should be repeated. After the injection, a transient burning sensation occurs; antibodies to botulinum toxin may appear. Recently, botulinum toxin has also been used successfully for spasms of multiple muscle groups, e.g., in the upper or lower extremities after a stroke, or in spasms that accompany childhood cerebral palsy.

Botulinum toxin can also be used to prevent excessive sweating (***hyperhidrosis***), via local injection, as it prevents cholinergic stimulation of the sweat glands. It is most often applied in the armpit area.

Table 9. Doses of antispasmodics.

DRUG	INDICATION	DOSE
Baclofen	Spinal spasticity	10 mg/day orally initially, then up 20 mg/8 h
Diazepam	Spasticity	4 mg/8 h orally
Dantrolen	Spasticity	25 mg/12 h initially orally, then up to 50 mg/6 h

ESSENTIAL TREMOR

Essential tremor is inherited in an autosomal dominant manner and most often manifests as trembling of the fingers and trembling of the entire hand at the wrist. In addition, head tremor or voice tremor occurs. Essential tremor is excellently treated with the beta-blocker **propranolol** (80-240 mg daily, divided into several doses). Small doses of ethyl alcohol also reduce tremor, but such therapy is not practical for other reasons (addiction).

In the treatment of essential tremor, **primidone**, a drug that is metabolized in the body to phenobarbitone, can also be used. The drug is effective, but side effects are particularly common in these patients (sedation and ataxia).

If essential tremor does not respond favorably to propranolol or primidone (30-50% of patients), it can be treated with the antiepileptic drugs **gabapentin or topiramate, the beta blockers atenolol or sotalol, or the benzodiazepine alprazolam**.

LOCAL ANESTHETICS

For the generation of an action potential in nerve fibers, it is necessary to open sodium channels in the fiber membrane. Local anesthetics block sodium channels on the cytoplasmic side and thus prevent the generation of an action potential, i.e., they interrupt the spread of information along the nerves. Local anesthetics first block unmyelinated and poorly myelinated nerve fibers (C and Adelta), and only later thick, fully myelinated fibers (Aalpha and Abeta fibers). Therefore, after the application of local anesthetics, the sensation of pain and heat is primarily lost, while the sensation of touch and the function of motor nerves are most often preserved.

There are two types of local anesthetics: ***esters*** (procaine, tetracaine, benzocaine, amethocaine) and ***amides*** (lidocaine, bupivacaine, levobupivacaine, ropivacaine, articaine, prilocaine and mepivacaine). The duration of action of local anesthetics depends primarily on the speed with which they are removed from the site of action, which is greatly influenced by the degree of vasodilation: by adding a vasoconstrictor (e.g. adrenaline) to the local anesthetic, the effect can be significantly prolonged. The action of esters lasts shorter (about 45 minutes) and because they are broken down by pseudocholinesterase from the blood plasma, and the action of amides is somewhat longer (about 1-1.5 hours), because they are broken down in the liver.

To achieve insensitivity to pain, local anesthetics are sprayed or instilled onto the surface of the mucous membrane (surface anesthesia), injected into the tissue (infiltration anesthesia), injected near the nerve trunks (conduction anesthesia), into the subarachnoid space (spinal anesthesia) or into the epidural space (epidural anesthesia). Numbness is achieved about 10 minutes after injection (therefore, after applying anesthetic, you should always wait those 10 minutes before starting the intervention!) and lasts about 1 hour. During this time, it is possible to perform a minor surgical intervention. The most commonly used superficial anesthesia are benzocaine (in the form of an oriblet, for anesthesia of the lacrimal mucosa of the oral cavity and pharynx), cocaine (in addition to acting as a local anesthetic, it also causes vasoconstriction in the mucous membrane), tetracaine (for corneal anesthesia) and benzydamine (as a spray for anesthesia of the oral mucosa).

If local anesthetics are overdosed (more than 600 mg of procaine or 400 mg of lidocaine), they cause changes in the CNS (dizziness, anxiety, confusion, tremor, even convulsions) and the cardiovascular system (tachycardia, hypotension, arrhythmias). While esters can cause allergic reactions, this is extremely rare with amides. Most often, patients become allergic to para-

aminobenzoic acid, which is a common metabolite of most ester local anesthetics. Fortunately, **there is no cross-allergy between amides and esters**; if someone is allergic to an ester local anesthetic, they can safely receive an amide local anesthetic, and vice versa. Bupivacaine shows particular toxicity among local anesthetics, as it binds with great affinity to the cardiac conduction system and causes serious ventricular arrhythmias. Therefore, less toxic drugs, such as its optical isomer levobupivacaine or its chemical analogue ropivacaine, are increasingly used instead of bupivacaine. Ropivacaine has less toxicity to the central nervous system and myocardium, and also shows a lower tendency to cause motor nerve block.

Articaine is a newer local anesthetic that stands out from other amide anesthetics in that it also has an ester group that is broken down by plasma esterases. Therefore, it is rapidly metabolized after entering the systemic circulation, and therefore has fewer toxic effects on the central nervous system and heart. Today, it is widely used for local anesthesia in dentistry, as well as in people with liver or kidney failure, the elderly, and children.

The already mentioned local anesthetic for surface application in the oral cavity, **benzydamine**, in addition to blocking sodium ion channels, also acts by inhibiting the synthesis of tumor necrosis factor alpha and interleukin 1, and to a lesser extent, it inhibits cyclooxygenase and lipoxygenase. Thus, in addition to its local anesthetic effect, this substance also has an anti-inflammatory effect.

Tetrodotoxin and saxitoxin

Two very potent natural poisons, tetrodotoxin and saxitoxin, act by a mechanism similar to that of local anesthetics. They also block Na+ channels, but do so from the outside of the membrane. Tetrodotoxin is found in the liver and ovaries of the Japanese "balloon fish" (this fish inflates like a balloon when threatened); saxitoxin is produced by microorganisms that make up plankton and accumulates in the tissues of shellfish. Both poisons cause paralysis.

GENERAL ANESTHESIA

General anesthesia is a state of CNS depression characterized by loss of consciousness and cessation of central processing of sensory information from the periphery (no response to pain, tendon reflexes cannot be elicited). It can be achieved with inhalation or intravenous anesthetics. Anesthesia has several phases that the patient goes through, depending on the dose of anesthetic. The first phase (analgesia phase) occurs at the beginning, while anesthetic concentrations in the blood are still low. The patient is fully conscious, but has lost the feeling of pain. With further use of anesthetics, the second phase occurs - the delirium phase. Then the patient is restless, with tense muscles, confused, able to get up from the operating table. In modern general anesthesia, this phase is practically eliminated by the rapid administration of drugs. The third phase of anesthesia is called surgical, because surgical interventions are performed in it. It is divided into 4 subphases that differ in the depth of CNS depression. When the corneal reflex is lost, the patient has reached the third subphase, and then the optimal conditions for surgical intervention have actually been achieved. We do not want to achieve a greater depth of anesthesia, because in the fourth phase, respiratory and cardiac depression occurs, which results in a lethal outcome.

When we introduce a patient into general anesthesia for any surgical intervention, we want to achieve the following: (1) rapid loss of consciousness; (2) sufficient depth of anesthesia to prevent reflex reactions to pain (e.g., reflex bradycardia during manipulation of the patient's intestines on the operating table); (3) minimal and reversible impact on vital physiological functions (respiration and cardiac activity); (4) relaxation of skeletal muscles; (5) rapid recovery from anesthesia, and (6) safety in the use of anesthetics (no risk of explosion or fire). Since none of the anesthetics known today can meet all of the above requirements, a combination of several anesthetics and other drugs is usually used; such general anesthesia is called ***balanced anesthesia***.

General inhalation anesthesia

Some gases (nitrous oxide, N_2O) and vapors of volatile liquids (ether, halothane, enflurane, isoflurane, sevoflurane, desflurane) that reach the bloodstream and then the CNS through inhalation and the alveolar-capillary membrane lead to depression of neuronal activity and anesthesia. The molecular mechanism of their action is still unclear. Gases and vapors are both taken in and eliminated through the lungs; only some of them (e.g. halothane) are partially metabolized in the liver.

The speed at which anesthesia will begin after the administration of the drug and the speed at which the patient will wake up after the drug is discontinued depends primarily on the solubility of the anesthetic in the blood and fatty tissue. Anesthetics that are poorly soluble in blood and fatty tissue (nitrous oxide) have a rapid onset and rapid cessation of action, as they easily lead to saturation of these media. On the other hand, anesthetics that are highly soluble in blood and fatty tissue (e.g. halothane) have a slow onset, a slow cessation of action (because a large amount of the drug has dissolved and requires more time for elimination) and cause a long-lasting "hangover" after the cessation of anesthesia (because they are very slow to withdraw from the fatty tissue in which they have accumulated in large quantities during anesthesia). According to **Henry's law**, the amount of gas that dissolves in a liquid is directly proportional to the partial pressure of the gas and the affinity of the gas for the molecules of the liquid (solubility). The anesthesiologist administers anesthetic gas or vapor by changing its partial pressure in the air that is pumped into the patient's lungs using a respirator on an anesthesia machine. At the beginning of anesthesia, the partial pressure increases, so that the gas or vapor passes into the blood (and from there into the tissues); when anesthesia is to be terminated, the supply of anesthetic gas or vapor is interrupted, so that it passes from the tissues into the blood, and from the blood into the alveolar air and then out. The partial pressure of a gas or vapor at which 50% of patients will not react by moving to a skin incision is called the minimum alveolar concentration (MAC). It is usually not expressed in units of pressure, but as a percentage of all gases in the mixture that the anesthesiologist pumps into the patient's lungs using a machine. MAC is an indicator of the strength of the anesthetic. For example, the MAC of sevoflurane is 2%, and the MAC of nitrous oxide is more than 100%. This means that we can achieve anesthesia with only 3-4% sevoflurane in the inhaled air, while we cannot do so even with 100% nitrous oxide (which is why nitrous oxide is never used alone, but in combination with other anesthetics).

Nitrous oxide is therefore not a strong enough anesthetic, so it cannot provide the necessary depth of anesthesia on its own; its effect must be enhanced by the simultaneous use of another inhalation anesthetic (for example, 40% nitrous oxide and 0.5% halothane), opiate analgesics (usually fentanyl), neuroleptics (most often droperidol) or a combination of these drugs (the combination of fentanyl and droperidol, known as Talamonal^{R}, is particularly frequently used). General anesthesia in which neuroleptics are used as an adjunct is called "neurolept anesthesia".

Nitrous oxide is usually used in concentrations of 25% to 40%, because then it has the strongest analgesic effect, and it deprimes the CNS without the undesirable excitatory phenomena that occur at higher concentrations (vomiting, restless patient). Since it does not cause respiratory and cardiac depression, it is considered a relatively safe general anesthetic, and is used alone in dentistry and in emergency centers to induce analgesia. It is then usually administered in a mixture with oxygen (50% nitrous oxide and 50% oxygen) called **entonox**. Excessive use of nitrous oxide is not desirable, as it interferes with the functioning of vitamin B_{12}, and can lead to megaloblastic anemia and leukopenia.

Nitrous oxide is popularly called "laughing gas", because at the beginning of its use, at lower concentrations, it leads to disinhibition and uncontrolled giggling in the person who inhales it. This phenomenon can be avoided by applying the gas more quickly.

Halothane, desflurane, sevoflurane, isoflurane and enflurane are halogenated hydrocarbons, which evaporate easily at room temperature. Halothane depresses the respiratory center and cardiovascular system (direct myocardial depression, inhibition of the baroreceptor reflex, hypotension), sensitizes the myocardium to catecholamines, and reduces coronary blood flow. It also reduces renal blood flow (thereby reducing diuresis), and increases cerebral blood flow and intracranial pressure. It is an extremely potent anesthetic (MAX=0.5%), but should be used with caution in individuals with heart disease, kidney disease, or CNS injury. Halothane is oxidized in the liver, forming toxic metabolites: trifluoroacetic acid, and free bromine and chlorine ions. Repeated anesthesia with halothane increases the risk of hepatitis, which is rare (1:35,000), but has a severe form.

Ether is an anesthetic that is almost not used today because it is explosive, irritates the respiratory tract and causes a pronounced delirious phase of anesthesia. However, it is a very safe anesthetic with which it is easy to regulate the depth of anesthesia and which can be applied in improvised conditions, without special equipment. That is why most armies in the world have it in their war reserves.

Enflurane, similar to halothane, depresses the cardiovascular system (direct myocardial depression, hypotension, but without blockade of the baroreceptor reflex) and sensitizes the myocardium to catecholamines. It can sometimes cause tonic-clonic seizures in patients under anesthesia. Since during its metabolism, a fluoride ion is released, which has a toxic effect on the kidney tubules, transient damage to kidney function can sometimes occur.

Isoflurane is an effective and low-toxic inhalation anesthetic: it does not depress the cardiovascular system, dilates the coronary arteries, and does not sensitize the myocardium to catecholamines. Also, its metabolism releases far fewer fluoride ions than enflurane. The downside of isoflurane is that it causes transient, mild tachycardia, due to direct sympathetic stimulation; caution should be exercised in people with coronary disease. It also causes irritation of the respiratory tract, but less than desflurane.

Sevoflurane is less soluble in the blood than other anesthetics in this group, so its onset of action is faster. It is more popular than other inhalation anesthetics because it does not irritate the respiratory tract. It causes vasodilation and a decrease in cardiac output, increases cerebral blood flow, and raises intracranial pressure. There is a suspicion that substances with nephrotoxic effects are formed in contact with carbon dioxide absorbents found in anesthesia machines. Sevoflurane can sometimes cause convulsions or agitation in children and adolescents.

Desflurane is similar to sevoflurane in terms of its solubility in the blood and speed of action. It depresses the cardiovascular system, like other halogenated hydrocarbons, and stimulates the sympathetic nervous system, causing sudden but transient tachycardia. The downside of desflurane is that it causes irritation of the respiratory tract.

Today, general anesthesia is never performed with just one inhalation anesthetic. Anesthesia is now usually initiated with the intravenous administration of the ultra-short-acting barbiturate thiopentone sodium or some other intravenous anesthetic; the patient loses consciousness almost immediately and enters the second phase of anesthesia. This allows the insertion of an endotracheal tube and then the administration of an inhalation anesthetic that further maintains the achieved depth of anesthesia (two inhalation anesthetics are often combined at lower partial pressures to avoid their side effects). For better muscle relaxation (which is necessary for the successful work of the surgeon), the patient is given neuromuscular blocking agents; they allow the anesthesiologist to reduce the depth of anesthesia (which means that the risk of cardiovascular depression will be lower) without making the surgeon's work more difficult. To prevent reflex activation of the autonomic nervous system due to pain, opioid analgesics (e.g. fentanyl) are added to the patient during anesthesia. As mentioned at the beginning of this chapter, such anesthesia in which an inhalation anesthetic is combined with other drugs is called "**balanced anesthesia**".

Malignant hyperthermia is one of the side effects of general inhalation anesthetics. It is believed to be caused by the uncontrolled release of Ca++ from the sarcoplasmic reticulum, which leads to muscle cell contraction, high energy expenditure, heat generation, and lactic acidosis. This dangerous condition is treated with **dantrolene**, a drug that prevents excessive release of Ca++ from the sarcoplasmic reticulum, as well as other nonspecific measures against acidosis and shock.

General intravenous anesthesia

General intravenous anesthesia is achieved with drugs that are administered intravenously, and have an anesthetic effect on the central nervous system. The common property of all intravenous anesthetics is liposolubility, so that after injection into a vein, they reach the CNS within seconds and achieve high concentrations in the brain tissue, which, due to its excellent blood supply, receives as much as ¼ of the heart's minute volume. Therefore, intravenous anesthetics very quickly lead to loss of consciousness. However, the effect of intravenous anesthetics is short-lived (patients wake up after about 15 minutes), because there is redistribution, i.e., the drug returns from the brain tissue to the blood, and then moves from the blood to less well-circulated tissues (muscle and fat).

Although their effect lasts for a short time, most intravenous anesthetics remain in the body for a long time, because they are slowly metabolized in the liver. This fact is not significant if these drugs are administered in a single dose, or for a short time, only to introduce the patient into general anesthesia; but, if they were used in the form of intravenous infusion, for a longer period, to introduce and maintain anesthesia throughout the entire surgical intervention, there is a possibility of accumulation in the body and delayed awakening of the patient after the cessation of drug administration. However, by precisely dosing intravenous anesthetics via intravenous infusion (today there are computer programs that can accurately calculate the required dose and rate of administration), it is possible to avoid excessive accumulation of these drugs, and maintain anesthesia long enough to perform shorter surgical interventions or painful and unpleasant procedures. Such a type of anesthesia is called **total intravenous anesthesia**, which is especially popular today for performing outpatient surgical interventions.

Ultra-short-acting barbiturates

Ultra-short-acting barbiturates include sodium thiopentone, sodium methohexital, and sodium thiamylal. They are used most often for induction of general anesthesia, and much less frequently for maintenance of anesthesia for short procedures, or for deepening anesthesia induced by other agents. The advantages of ultra-short-acting barbiturates are: rapid and pleasant induction of anesthesia, rare induction of vomiting, and the fact that they do not sensitize the myocardium to catecholamines or increase secretion in the respiratory tract. Adverse effects of these drugs include myocardial depression and venous dilation (reducing cardiac output), respiratory depression, and sometimes laryngospasm.

Of the three ultra-short-acting barbiturates mentioned, only **methohexital** stands out, due to its half-life than the others, and its lower tendency to accumulate in the body with prolonged use.

Benzodiazepines

Of all the benzodiazepines, midazolam is the most widely used for intravenous anesthesia, primarily due to its short-acting nature and water solubility (the intravenous preparation contains water as a solvent, so it does not irritate the vein wall during injection). Unlike other intravenous anesthetics, midazolam is rapidly metabolized in the liver, so its half-life is only 1-2 hours.

Midazolam is used primarily for conscious sedation, necessary for short, unpleasant interventions. The patient does not lose consciousness completely, and can respond to verbal commands, while at the same time tolerating unpleasant and painful procedures (e.g. bronchoscopy, dressing, etc.). Midazolam, when properly dosed, does not cause depression of the heart or breathing, which, along with anterograde amnesia (the patient later does not remember the unpleasant procedure he underwent), is an additional advantage.

Recently, a new benzodiazepine anesthetic, **remimazolam**, has been used, whose effect begins even faster, lasts shorter, and recedes more quickly than that of midazolam. Remimazolam is broken down by tissue esterases.

Propofol and ciprofol

Propofol is a short-acting intravenous anesthetic that is rapidly metabolized in the liver and other tissues to inactive metabolites. It is used to induce anesthesia, to maintain anesthesia with opioids, for conscious sedation, and as an adjunct to general inhalation anesthesia. Propofol has an antiemetic effect.

Propofol depresses the heart and respiration, leading to hypotension; however, reflex tachycardia does not occur because baroreceptors are also inhibited. In addition, the use of propofol may be (albeit very rarely) associated with the occurrence of convulsions and arrhythmias. When administered intravenously, the drug may cause irritation of the vein wall and pain, so administration through smaller veins should be avoided.

Ciprofol is chemically related to propofol and acts as a GABA receptor agonist. It is five times more potent than propofol, disrupts the patient's hemodynamics less, and does not cause pain during intravenous injection..

Etomidate

Compared to barbiturates and propofol, etomidate is a safer drug to use, as it does not cause significant depression of heart rate or breathing, with a slight dilation of the coronary arteries. Like propofol, it is also metabolized relatively quickly in the liver (half-life about 3 hours), so it does not tend to accumulate with prolonged use. It is used to induce anesthesia in patients, and as an adjunct to anesthesia induced by other agents.

The disadvantages of etomidate are the occurrence of **myoclonic seizures** in about 42% of patients, irritation of the vein at the site of administration, and **transient suppression of the adrenal gland**, which cannot respond to stress by releasing sufficient amounts of hormones (due to the pyrrole ring in the etomidate molecule).

Ketamine

Ketamine is an intravenous anesthetic with a chemical structure related to the psychotomimetic phencyclidine, which does not have a depressant effect on heart rate and blood pressure. There is even a transient increase in blood pressure and an acceleration of heart rate, due to sympathetic stimulation. Respiratory depression occurs only when very high doses are used.

The anesthesia induced by ketamine resembles a trance state (e.g.. the patient appears awake, with open eyes, and does not react to stimuli) and is accompanied by an increase in muscle tone (it also resembles catatonia). Pharyngeal and laryngeal reflexes are also preserved. The pronounced analgesic effect of ketamine is particularly significant.

Its use is indicated in children and the elderly, whose cardiovascular system is particularly sensitive to the use of CNS depressants. A dose of 2 mg/kg of body weight administered intravenously leads to a state of anesthesia in about 60 seconds, lasting 5-10 minutes. The advantage of ketamine is also the possibility of intramuscular administration.

Ketamine is used as an anesthetic for short interventions outside the operating room due to its cardiovascular stability and preservation of laryngeal and pharyngeal reflexes.

When it comes to side effects, ketamine causes nightmares and an unpleasant feeling of separation from one's own body after waking up. That is why ketamine anesthesia is called „dissociative anesthesia“ („separating“). Sometimes patients are restless, cry and shout. Fortunately, such effects are less common in children and the elderly than in other age categories.

Intravenous anesthesia with opioids

Phenylpiperidine opioids (fentanyl, sufentanil, alfentanil and remifentanil) are also used to induce general anaesthesia in patients, and also to maintain general anaesthesia in shorter procedures. For these purposes they are used in high doses, about 10 times higher than analgesic doses.

Opioids do not cause myocardial depression and hypotension, but they significantly depress respiration. This is partly due to depression of the respiratory centre in the medulla oblongata, and partly to stiffness of the chest and abdominal muscles. Therefore, it is necessary to artificially ventilate the patient after their administration.

A particular problem with the use of opioids is the possibility that a sufficient depth of anaesthesia may not be achieved in some patients, so they may wake up during the operation or hear the conversation of the surgical team.

Total intravenous anesthesia (TIVA) refers to the modern use of intravenous anesthetics, often in combination, using infusion pumps and monitoring the depth of anesthesia. This method of administration is significantly safer for the patient, and the required depth and duration of anesthesia are achieved.

PHARMACOLOGY OF CARDIOVASCULAR SYSTEM

ANTIHYPERTENSIVES

In most patients with hypertension (90%), the exact cause cannot be determined and then we speak of essential hypertension. Based on the severity of the clinical picture, hypertension is classified into prehypertension (diastolic pressure 85-89 mmHg, systolic 130-139 mmHg), stage 1 hypertension (diastolic pressure 90-99 mmHg, systolic pressure 140-159 mmHg) and stage 2 hypertension (diastolic pressure > 100 mmHg, systolic pressure > 160 mmHg). Hypertension must be treated because it leads to serious complications in the heart, kidneys and eye fundus.

When prehypertension is present, medication is not necessary; stage 1 hypertension is treated with a single drug, and stage 2 hypertension with a combination of drugs.

Hypertension can be treated in several ways: 1) by reducing the activity of the sympathetic nervous system 2) by reducing intravascular volume and 3) by vasodilation, i.e., by reducing peripheral resistance.

Reducing the activity of the sympathetic nervous system can be achieved by acting on the cardiovascular center in the medulla oblongata or by peripheral action.

Alpha-methyldopa and clonidine are agonists of presynaptic alpha2 receptors in the cardiovascular center of the medulla oblongata (alpha-methyldopa only after it is converted into the active form, alpha-methylnoradrenaline, in the body), which reduce the activity of this center, and thus the entire sympathetic nervous system. They are used to treat moderately severe hypertension, only after other drugs have proven ineffective, because they have many side effects.

Both drugs, by reducing sympathetic activity, reduce peripheral resistance to blood flow and cardiac output. They do not reduce renal blood flow or glomerular filtration, which makes them useful drugs for hypertension in patients with reduced renal function. However, after prolonged use, they lead to water and sodium retention; therefore, they are generally not used alone, but in combination with diuretics.

If administered intravenously, clonidine can cause a short-term increase in blood pressure, due to direct stimulation of peripheral alpha-receptors. Such an effect does not occur with oral administration.

Alpha-methyldopa and clonidine cause sedation and drowsiness, dry mouth, nasal congestion, orthostatic hypotension, depression and impotence. Alpha-methyldopa also sometimes causes hemolytic anemia, thrombocytopenia or leukopenia. Clonidine also causes constipation and nausea. Clonidine should not be discontinued abruptly, as it may cause a sudden worsening of hypertension (patients should be especially warned about this fact!).

This group of drugs also includes **moxonidine**, which also stimulates alpha 2 receptors in the central nervous system, but also additionally stimulates **imidazoline receptors**. Since it stimulates alpha receptors less than imidazoline receptors, it does not have some of the side effects of alpha-methyldopa and clonidine: dry mouth and drowsiness.

Drugs that interfere with the functioning of adrenergic neurons also reduce the activity of the sympathetic nervous system. Some of them, such as **guanethidine and bretylium**, prevent the release of transmitters from postganglionic sympathetic neurons, others empty the stores of noradrenaline in the nerve endings (e.g., **reserpine**), and still others reduce the synthesis of noradrenaline (**metyrosine**).

Guanethidine is taken up into the endings of adrenergic neurons by the same mechanism by which noradrenaline is taken up. In the endings themselves, it then prevents the release of noradrenaline when the action potential reaches the ending. Guanethidine is used to treat severe hypertension that does not respond to other drugs.

Reserpine blocks the transport of noradrenaline and dopamine from the cytoplasm to the presynaptic vesicles, causing them to be degraded by monoamine oxidase. The end effect is a decrease in the amount of neurotransmitters and impaired transmission in the sympathetic nervous system, as well as in the dopaminergic and noradrenergic pathways in the brain. Reserpine was once used as a drug for severe forms of hypertension, but was withdrawn from use due to side effects.

Due to the blockade of dopaminergic pathways in the brain, reserpine can cause depression, sedation, nightmares and suicidal thoughts. Extrapyramidal syndrome is also possible. Like guanidine, reserpine causes nasal congestion, impotence, increased secretion of stomach acid and diarrhea (due to the predominance of the parasympathetic).

Metyrosine (alpha-methyl tyrosine) blocks the enzyme tyrosine hydroxylase, which prevents the synthesis of noradrenaline and adrenaline. It is used extremely rarely, in patients with inoperable pheochromocytoma. It is administered orally; it is not metabolized, but is excreted unchanged in the urine.

The main side effects of metyrosine are sedation, confusion, disorientation, and nasal congestion.

Peripheral sympathetic blockade is also achieved by the use of alpha-blockers or beta-blockers. **Beta-blockers (propranolol, metoprolol)** reduce cardiac output and renal renin release, which leads to a decrease in peripheral resistance due to a decrease in the level of angiotensin 2 in the blood. They are most often used for the treatment of hypertension in younger people with healthy myocardium. Due to their negative inotropic and negative dromotropic effects, in higher doses in older people with heart disease they can lead to heart failure or some form of impulse conduction block. They should be avoided in patients with bronchial asthma, diabetes and arteriosclerosis in the extremities, because by blocking beta2-receptors they lead to bronchoconstriction, inhibition of insulin release and vasoconstriction of the arteries of the extremities. However, beta-blockers are usually well tolerated.

Combinations of beta-blockers with diuretics or vasodilators have proven to be very effective in practice. In addition, beta-blockers suppress the undesirable effect of vasodilators: reflex tachycardia.

Alpha-blockers (primarily selective alpha1-blockers, prazosin, terazosin and urapidil) lead to vasodilation of arteries and arterioles, a decrease in peripheral resistance and a decrease in blood pressure. Also, due to the blockade of alpha-receptors in the walls of venules and veins, the inflow of venous blood into the heart is reduced, and thus the stroke volume. Although much less frequently than non-selective alpha-blockers, these drugs can also lead to reflex tachycardia due to a decrease in the activation of baroreceptors in the aortic arch and carotid sinus. In addition, they interfere with normal ejaculation and can lead to fluid retention due to reduced blood flow through the kidneys. They are used to treat moderate hypertension, usually in combination with drugs that work by a different mechanism. The doctor must explain to the patient who is prescribed prazosin that he should first start with a low dose (1 mg) that should be taken just before bedtime; if he does not do this, severe hypotension may occur after the first dose (because the body has not yet adapted), and even syncope (loss of consciousness due to a sudden decrease in blood flow through the brain). The good side of alpha-blockers is their beneficial effect on blood lipids. It is useful to combine these drugs with thiazide diuretics and beta-blockers, because the former prevent water and sodium retention, and the latter reflex tachycardia.

Urapidil is the only drug in this group that is administered parenterally for the treatment of hypertensive crisis. Due to its additional central effects (the mechanism of which is not yet clear), this drug does not cause reflex tachycardia, which is a great advantage.

Intravascular volume depletion is achieved by the use of **diuretics, most often thiazides or loop diuretics**. This effect is transient, so that after a few weeks the intravascular volume returns to the initial level. However, the hypotensive effect remains, probably due to the **direct vasodilator effect of the diuretic**. Diuretics are usually used to treat mild hypertension in the elderly. When they are used, the level of K+ ions in the blood should be controlled; if hypokalemia occurs, it is necessary to administer a potassium preparation orally. Thiazides can worsen glycemia in diabetics, and hyperuricemia in people prone to gout. If the patient has renal insufficiency, only loop diuretics should be used, as thiazides are not effective.

Several years ago, aldosterone receptor-blocking diuretics were approved for use in the treatment of hypertension resistant to first-line antihypertensives (beta-blockers, thiazide diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin 2 receptor blockers). This group of drugs includes **spironolactone, esaxerenone, and finerenone**. They are used as an add-on therapy to an existing combination of three first-line antihypertensives (i.e., as a fourth drug).

Vasodilation is caused by drugs directly or indirectly. Minoxidil, hydralazine, diazoxide, and calcium channel blockers act directly on arteries and arterioles; sodium nitroprusside acts on both arteries and veins. Vasodilators are used to treat moderate and severe hypertension, but only in combination with diuretics (if used alone, they cause fluid retention due to reduced blood flow through the kidneys). It is desirable to simultaneously administer a beta-blocker to prevent reflex tachycardia; due to strong vasodilation, baroreceptor activity decreases, so the use of vasodilators alone is accompanied by tachycardia. **Minoxidil** opens K+ channels and hyperpolarizes the membrane of smooth muscle cells of blood vessels, leading to their relaxation. Minoxidil is used to treat severe, resistant hypertension. The good thing about all vasodilators is that they are always active, regardless of the mechanism of hypertension.

In addition to reflex tachycardia, minoxidil causes nasal congestion and headache. It also increases hair growth, which in women can result in increased hair loss. This effect on hair has been used to produce various lotions (including minoxidil) that promote hair growth in baldness.

Hydralazine is another orally administered vasodilator. It works by opening potassium ion channels in the membrane of smooth muscle cells, and by releasing nitric oxide from endothelial cells (which then acts as a relaxant on smooth muscle).

Hydralazine is well absorbed after oral administration. It is metabolized in the liver, first by hydroxylation, and then by glucuronidation and acetylation. However, most of the drug undergoes the process of acetylation, which takes place not only in the liver but also in the mucous membrane of the small intestine. There are people who have damaged genes that regulate the acetylation process, so that the amount of the enzyme that performs acetylation is too low. In such people (so-called "**slow acetylators**"), hydralazine is eliminated much more slowly, so its effect is prolonged and intensified. Hydralazine metabolites and a small amount of unchanged drug (10%) are eliminated in the urine. The effect of hydralazine lasts for 6 hours.

Hydralazine, like other vasodilators, reduces peripheral resistance to blood flow. Its simultaneous use with a diuretic (to prevent sodium retention) and a beta-blocker (to prevent reflex tachycardia) is recommended.

Side effects of hydralazine include headache, facial flushing, nasal congestion, and reflex tachycardia. If used for a long time, it causes a condition similar to systemic lupus erythematosus in a number of patients..

Sodium nitroprusside increases the amount of cGMP in smooth muscle cells, which leads to their relaxation. It relaxes both arteries and veins, so it has a hypotensive effect, but also reduces blood flow to the heart. Therefore, it has a beneficial effect on both hypertension and acute heart failure. Sodium nitroprusside is used to treat hypertensive crisis in the form of an i.v. infusion. It spontaneously breaks down in the blood, so its effect quickly ceases; this is the reason why it is administered as an intravenous infusion. By changing the infusion rate, we can lower or increase blood pressure. After the infusion stops, the effect of the drug is lost in 2-3 minutes.

A special problem with the use of sodium nitroprusside is the accumulation of cyanide and thiocyanate, which are created by the breakdown of this drug. Cyanides cause metabolic acidosis, dyspnea, headache, and loss of consciousness. Thiocyanates can cause delirium. To prevent this, the infusion rate should not exceed 10 mcg/kg/min.

Diazoxide is chemically related to thiazide diuretics, but instead of increasing sodium excretion, it causes sodium and water retention. It causes relaxation of smooth muscle cells of arterial blood vessels by opening potassium channels. This results in hypotension, but with reflex activation of the sympathetic nervous system.

Diazoxide is administered intravenously for the treatment of hypertensive crisis. After administration, the hypotensive effect begins within 5 minutes and lasts up to 12 hours. Since the administration of diazoxide will cause reflex activation of the sympathetic nervous system, people with coronary artery disease should be given a beta-blocker at the same time, which will prevent the effect of the sympathetic nervous system on the heart.

Due to its similarity to thiazides, diazoxide also has the following side effects: hyperglycemia and hyperuricemia.

Calcium channel blockers (amlodipine, lecarnidipine, nifedipine, diltiazem) are used as vasodilators for the treatment of mild hypertension. They are well tolerated. Nifedipine can also be used for the treatment of milder forms of hypertensive crisis. In this case, it is administered sublingually, in a dose of 10-20 mg.

Indirect vasodilation is caused by drugs that block the renin-angiotensin system. There are three groups of these drugs: drugs that inhibit angiotensin-converting enzyme (convertase, peptidyl dipeptidase), drugs that block angiotensin 2 receptors, and drugs that inhibit the action of renin. Drugs that inhibit convertase are called **angiotensin-converting enzyme inhibitors, or ACE inhibitors for short**. This enzyme is found in the endothelium of the lungs and converts angiotensin 1 to angiotensin 2, one of the most potent vasoconstrictor substances, and also breaks down bradykinin (a peptide with a pronounced vasodilating effect). Due to the decrease in angiotensin II levels and the increase in bradykinin levels after the administration of **captopril, enalapril,**

ramipril, lisinopril, quinapril and other drugs from this group, vasodilation, a decrease in peripheral resistance and a decrease in blood pressure occur. These drugs also increase cardiac output, by reducing both preload and afterload on the heart; myocardial thickness is also reduced, i.e. hypertrophy is reversed.

Captopril is administered orally. The hypotensive effect begins after 15 minutes, reaches a maximum after 45 minutes, and lasts about 6-8 hours. The drug is inactivated in the kidneys.

These drugs are used to treat mild to moderate hypertension, but only on condition that renal artery stenosis is previously excluded; in the event of stenosis, ACE inhibitors can cause acute renal failure. In addition to treating hypertension, angiotensin-converting enzyme inhibitors are also used to treat heart failure. They are therefore combined with thiazide diuretics, because such a combination, in addition to its additive effect on heart failure, has another advantage: thiazides lead to hypokalemia, and ACE inhibitors tend to raise serum potassium levels, so potassium concentrations remain within normal limits.

ACE inhibitors are particularly useful in people who, in addition to hypertension or heart failure, also have type 1 diabetes mellitus. They slow down the progression of nephropathy and delay the onset of kidney failure.

Captopril, as an older drug, has several side effects: it causes neutropenia, metallic taste, edema, and worsens asthma. Enalapril, ramipril, cilazapril, quinapril, fosinopril, and other newer drugs do not have a toxic effect on the bone marrow. Due to the blockade of angiotensin 2 synthesis, aldosterone synthesis is reduced, so these drugs can lead to hyperkalemia. However, the side effect that most often causes patients to stop taking the drug is a persistent dry cough (since the convertase that normally breaks down bradykinin in the respiratory tract no longer functions, bradykinin accumulates and causes cough).

ACE inhibitors can cause severe hypotension at the first doses, so treatment is always started at a lower dose. During their use, it is necessary to monitor kidney function and reduce the dose if it worsens. Due to the possibility of causing angioedema (due to the accumulation of bradykinin), ACE inhibitors should not be used in people with congenital or idiopathic angioedema.

ACE inhibitors should also not be used in pregnant women, as they are teratogenic and fetotoxic.

Recently, **angiotensin II AT1 receptor blockers**, **losartan, valsartan, telmisartan, eprosartan, candesartan and irbesartan**, have also been used to treat hypertension and heart failure. These drugs are currently only given to patients who have previously been successfully treated with angiotensin converting enzyme inhibitors, but had to discontinue therapy due to persistent cough. In one of the clinical studies, 150 mg/day of irbesartan led to a mean decrease in systolic/diastolic blood pressure of 10/5 mmHg after 6 weeks. Side effects of these drugs are hypotension, hyperkalemia and the appearance of angioedema. They should be used with caution if there is renal artery stenosis! (see convertase inhibitors!) They are also contraindicated during pregnancy, due to teratogenic and fetotoxic effects. All AT1 receptor blockers are administered orally. Losartan and candesartan are transformed into active metabolites in the liver, while other drugs from this group do not have active metabolites. The effect of losartan lasts the shortest (6-8 hours), and telmisartan the longest.

Aliskiren is a drug that inhibits the action of renin on angiotensinogen, thereby preventing the synthesis of angiotensin 1. Aliskiren is as effective in treating hypertension as ACE inhibitors, beta blockers, diuretics, and calcium channel blockers. It can be used alone or in combination with diuretics, beta blockers, or calcium channel blockers. It is administered orally, once daily. A common side effect of aliskiren is hyperkalemia, and sometimes worsening of kidney function may occur, especially in people who are hypovolemic, have diabetes, liver disease, or already have impaired kidney function. Aliskiren can also cause angioedema.

Aliskiren is poorly absorbed from the digestive tract (bioavailability is 2-3%), but it penetrates well into tissues. It is mostly excreted unchanged in the feces, and about 1.4% of an orally administered dose is metabolized by cytochrome CYP 3A4. The half-life of aliskiren is about 40 hours, which allows it to be used in a once-daily dose.

Choice of antihypertensives

The choice of antihypertensive drug depends primarily on the characteristics of each individual patient: concomitant diseases or conditions in patients that affect the efficacy and side effects of drugs must be taken into account.

Mild hypertension (stage 1) is usually treated with a single drug; moderate to severe hypertension (stage 2) is treated with a combination of two or more drugs that act by different mechanisms. In resistant hypertension, which does not respond to the use of three first-line drugs, a fourth drug from the group of aldosterone receptor blockers is added.

Treatment of hypertension in special types of patients

In the elderly, antihypertensives should be used if diastolic blood pressure is greater than 90 mmHg or systolic blood pressure is greater than 160 mmHg during 6 months of observation. The drugs of choice for elderly patients are thiazide diuretics; if the effect is not achieved, beta-blockers are added.

In insulin-dependent diabetics, the drugs of choice for the treatment of hypertension are ACE inhibitors, because they slow the progression of nephropathy. ACE inhibitors are even given to patients with type 1 diabetes who have normal blood pressure, provided that there is proteinuria. Diabetics with type 2 disease can be successfully treated with thiazides, beta-blockers, calcium channel blockers, or ACE inhibitors.

In renal failure, thiazide diuretics often do not work, so it is necessary to use a loop diuretic.

In pregnancy, the drug of choice for the treatment of hypertension is methyldopa, as it carries the lowest risk of congenital anomalies. In addition to this drug, nifedipine can be used; beta-blockers can only be used in the first trimester of pregnancy. Hydralazine is used to treat blood pressure spikes in preeclampsia.

Treatment of hypertensive crisis

A sudden increase in blood pressure may be asymptomatic, when this condition is called a "**hypertensive emergency**," or it may be accompanied by neurological symptoms or acute heart or kidney damage, when this condition is called a "**hypertensive crisis**." A hypertensive emergency can be treated outside the hospital with oral ACE inhibitors (e.g., captopril 25 milligrams), nifedipine in the form of a delayed oral formulation (20 mg), or labetalol (200-400 milligrams). These drugs are relatively short-acting, so chronic therapy should be started after the pressure has decreased. There should be no attempt to lower blood pressure abruptly to normal values, as this may do more harm than good. A sudden drop in blood pressure can lead to ischemia of vital organs and the appearance of symptoms.

A patient with a hypertensive crisis should be hospitalized immediately, preferably in an intensive care unit, and parenteral antihypertensives should be administered: sodium nitroprusside, labetalol, or urapidil.

Table 10. Doses of the most commonly used antihypertensive drugs.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Propranolol	oral	80 mg	12 h
Methyldopa	oral	500 mg	12 h
Prazosin*	oral	3 mg	8 h
Nifedipine	oral	10 mg	8 h
Hidralazine	oral	10 mg	6 h
Enalapril	oral	2.5 mg	12 h
Diazoxid**	i.v.	100 mg	15-30 min, total dose should not be > 300 mg
Nitroprusside sodium**	i.v. infusion	1-5 μg/kg/min	Protect infusion bottle and set from light

* The first dose should be small (1 mg), and taken immediately before bedtime due to the risk of excessive hypotension.

** Used for the treatment of hypertensive crisis.

TREATMENT OF PULMONARY HYPERTENSION

Pulmonary hypertension is caused by increased resistance to blood flow through the pulmonary artery network. Patients become dyspnoeic on exertion; over time, high pulmonary artery pressure leads to right ventricular failure. Without treatment, patients may live only a few years. Most patients have elevated serum levels of endothelin 1, a peptide paracrine factor that causes vasoconstriction.

Four groups of drugs are used to treat pulmonary hypertension: endothelin 1 receptor blockers, drugs that increase the concentration of cyclic guanosine monophosphate (cGMP), prostaglandin analogs, and blockers of activin A and other ligands from the transforming growth factor beta (TGF beta) superfamily.

Three **endothelin receptor blockers** are currently in use: **bonsetan**, which nonselectively blocks endothelin A and B receptors, and **ambrisentan and macitentan**, which selectively block mainly endothelin A receptors. Previous experience with

bonsetan has shown that it should be used in primary pulmonary hypertension and in pulmonary hypertension caused by scleroderma. The drug reduces dyspnea, patients are able to move for longer, and exacerbations are less frequent. Four years after the introduction of bonsetan into therapy, about 85% of patients survive. It is administered orally.

The side effects of bonsetan are serious: 11% of patients have elevated transaminases, and 6% of patients develop anemia. Some patients experience hypotension, flushing, and palpitations.

The advantage of ambrisentan and macitentan is their selectivity for A receptors, since activation of endothelin B receptors leads to the production of the vasodilators nitric oxide and prostacyclin. However, their effects in clinical studies were very similar to those of bonsetan. They are administered orally, and have similar side effects as bonsetan: they increase transaminase levels, cause anemia, and lead to the development of peripheral edema. However, macitentan seems to have somewhat less hepatotoxicity than the other two drugs.

Of the drugs that increase cGMP concentration, the first to be used were **phosphodiesterase type 5 inhibitors: sildenafil and tadalafil**. They reduce dyspnea and allow patients to move for longer, but there is still no evidence that they affect the length of survival. Their advantage is that they are administered orally and have few side effects. Recently, **a drug that directly stimulates guanylate cyclase to produce more cGMP has been introduced into therapy: riociguat**. Riociguat has proven to be more effective than phosphodiesterase inhibitors, as it increases the quality of life of patients and allows them to move for longer. The only serious side effect of this drug observed so far is an increased frequency of hemoptysis. Riociguat is administered orally.

The prostacyclin analog, iloprost, is administered by inhalation. It dilates arterioles and venules, reduces platelet aggregation, and reduces capillary permeability. Iloprost is inhaled 5-6 times a day, increases the functional capacity of patients with pulmonary hypertension, reduces exacerbations, but there is no evidence that it affects survival. As for side effects, iloprost causes hypotension, cough, headache, and rarely bronchospasm and bleeding from peptic ulcers.

Epoprostenol is a prostaglandin produced by endothelial cells. Epoprostenol inhibits platelet aggregation and has a vasodilating effect on the blood vessels of the pulmonary circulation. It is administered as an intravenous infusion in patients who have not responded to other drugs for pulmonary hypertension. Epoprostenol only leads to functional improvement in patients with pulmonary hypertension. As for side effects, it causes headache, facial flushing and thrombocytopenia.

Activin A blockers currently have only one representative – sotatercept - csrk. By blocking activin A and other ligands of the TGF beta superfamily, sotatercept reduces endothelial cell proliferation, thereby reducing resistance to blood flow in the pulmonary circulation. It is the first approved drug for pulmonary hypertension that has the potential to slow the progression of this disease. The most serious side effects of sotatercept are **erythrocytosis, thrombocytopenia**, and bleeding.

DIURETICS

Diuretics are drugs that increase urine output, and are used to remove excess extracellular fluid, along with its electrolytes. According to their mechanism of action, they are divided into several groups:

Thiazide diuretics. These drugs, chemically related to sulfonamides, are secreted in the proximal tubules (as weak acids, they use the anionic system of tubular secretion), reach the distal tubules and block the reabsorption of Na+ and Cl- ions there (the so-called co-transport of sodium and chlorine is blocked). These ions draw water with them, which results in an increase in the amount of urine. In an attempt to retain as much sodium as possible, the final parts of the distal tubules and collecting ducts exchange Na+ ions for K+ ions, so the use of thiazides leads to hypokalemia. Thiazides are used to treat mild edema (in heart failure, cirrhosis, etc.) and mild hypertension. Since they reduce calcium secretion in the kidney, they can also be used to treat renal calculi. Also, thiazide diuretics can paradoxically reduce the excretion of dilute urine in nephrogenic diabetes insipidus. Indapamide, metolazone, chlorthalidone and kinetazone act similarly to **thiazides (chlorothiazide, polythiazide, hydrochlorothiazide, methyclothiazide)**. We call them "thiazide-like" diuretics, which do not have a benzothiadiazine ring in their molecule, but act in the same way as thiazides. In addition to hypokalemia, the side effects of these drugs include hyperglycemia, hyperlipidemia and hyperuricemia. Remarkably, indapamide does not cause hyperglycemia.

The maximum effect of thiazide diuretics (achieved with maximum doses), in terms of urine volume, reaches about 5% of the ultrafiltrate, i.e. the fluid filtered in the glomeruli. This practically means that they can increase urine output by only a few liters.

Thiazide and similar diuretics are rapidly absorbed after oral administration, and begin to have a noticeable effect after only one hour. They are mostly eliminated in the urine, but a part of the administered dose is excreted in the bile, using the mechanism of bile acid secretion; this elimination pathway becomes especially important in renal failure. The effect of thiazide diuretics lasts on average up to 12 hours, so most of these drugs are administered in a single daily dose.

Interestingly, thiazide diuretics are useful in the treatment of nephrogenic diabetes insipidus. They moderately reduce glomerular filtration, and thus water excretion, which can somewhat improve the patient's condition.

Loop diuretics. Drugs in this group (**furosemide, bumetanide, torsemide, and ethacrynic acid**) are also secreted in the proximal tubule, but act on the thick, ascending limb of the loop of Henle, preventing the reabsorption of Na+, K+, and Cl-. They inhibit a transporter that reabsorbs one Na+ ion, one K+ ion, and two Cl- ions together. As much as 20% of the sodium filtered in the glomerulus is reabsorbed by this transporter.

Loop diuretics are significantly more effective than thiazides. They are used to treat severe edema, moderate to severe hypertension, pulmonary edema due to left heart failure, and hypercalcemia (because they reduce Ca++ reabsorption) with the use of saline infusion. Sometimes these diuretics, if administered early enough, can prevent the onset of acute renal failure due to hemoglobinuria (e.g., in transfusion reactions) or myoglobinuria (in crash syndrome). By increasing the flow of primary urine through the tubules, they can "flush" at least some of the hemoglobin and myoglobin out of the kidneys and prevent tubule blockage. Loop diuretics cause hypokalemia, transient hearing loss (if administered too rapidly intravenously), hyperuricemia (increased uric acid levels), and hyperglycemia. Only ethacrynic acid (whose molecule has no similarity to other diuretics in this group and sulfonamides) does not cause hyperglycemia. If overdosed, severe hypotension and impaired consciousness due to electrolyte imbalance occur.

Unlike thiazides, loop diuretics can also be effective in people with kidney failure.

All diuretics in this group can be administered both orally and parenterally. Their effect begins quickly, 5 minutes after intravenous administration, and 30 minutes after oral administration. Maximum diuresis is achieved after 2 hours, and the effect lasts for 6-7 hours. They are highly bound to plasma proteins. They are excreted in the urine mainly by tubular secretion; one third of the drug dose is excreted in the bile. Loop diuretics are not metabolized in the liver to any significant extent.

Carbonic anhydrase inhibitors. Acetazolamide and similar drugs (**methazolamide, dichlorphenamide**) inhibit the enzyme carbonic anhydrase, which enables bicarbonate reabsorption in the proximal tubules. Bicarbonates remain in the lumen of the tubules, drag Na+ ions and water molecules with them, and lead to a slight increase in diuresis. The diuretic effect of acetazolamide is weak (at most about 5% of the sodium ions filtered in the glomeruli can be excreted) and transient (it disappears after a few weeks), so this drug is not used as a diuretic. It is used primarily for the treatment of glaucoma (because it reduces the production of aqueous humor), pancreatitis (because it reduces the production of pancreatic juice), and for the prevention of altitude sickness. Exceptionally, epileptic seizures that occur in women during menstruation respond well to acetazolamide. Adverse effects of acetazolamide include hyperchloremic acidosis, hypokalemia (in addition to carbonic anhydrase inhibition, potassium ion reabsorption in the distal tubule and collecting ducts is reduced) and neurological disorders (paresthesias, confusion, ataxia, tingling in the extremities, loss of appetite).

Potassium-sparing diuretics. Drugs in this group act on the collecting ducts of the kidneys, where they interfere with the reabsorption of Na+ and the excretion of K+. They do this either by blocking the receptors for aldosterone, a hormone of the adrenal cortex responsible for the reabsorption of Na+ and the excretion of K+ (**spironolactone, eplerenone, exaxerenone, and finerenone**), or by blocking the Na+ channels in the collecting ducts (**triamterene and amiloride**). Potassium-sparing diuretics also inhibit the secretion of hydrogen ions (H+) in the collecting ducts.

Spironolactone is used to treat primary (Conn's syndrome) and secondary hyperaldosteronism (in cirrhosis of the liver, nephrotic syndrome, resistant hypertension, and congestive heart failure). Triamterene and amiloride are used when there is a risk of hypokalemia due to previous use of thiazide or loop diuretics; very often, medications containing a combination of thiazide diuretics and triamterene or amiloride are used from the beginning of therapy, thus preventing the occurrence of hypokalemia.

Side effects of these diuretics are hyperkalemia, metabolic acidosis (because inhibition of Na+ reabsorption reduces excretion except for K+ and H+) and neurological disorders (paresthesia, depression). Spironolactone also blocks androgen receptors, so it can cause **gynecomastia and impotence** in men, and menstrual cycle irregularities in women. Eplerenone, finerenone and exaxerenone cause gynecomastia and impotence much less often.

Osmotic diuretics. Osmotic diuretics are substances that, after administration, are filtered through the glomeruli of the kidneys and are not reabsorbed from the lumen of the renal tubules. By remaining in the lumen of the tubules, osmotic diuretics increase the osmolarity of the primary urine and thus prevent the reabsorption of water. The result is the excretion of a large amount of dilute urine.

Table 11. Doses of the most commonly used diuretics.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Hydrochlorthiazide	oral	50 mg	12 h
Indapamide	oral	2.5 mg	24 h
Furosemide	i.v..	20 mg	12 h
	oral	40 mg	12-24 h

Amilorid	oral	10 mg	24 h
Spironolactone	oral	100 mg	24 h
Acetazolamide	oral	250 mg	12 h
Mannitol	20% solution, i.v. infusion	12.5 g	*

* A test dose of 12.5 g is administered first; if diuresis increases to 50 ml/h or more over the next 3 hours, then another 12.5 g can be administered.

Mannitol is most commonly used today as an osmotic diuretic (glycerol, isosorbide, and urea were also used in the past; glycerol and isosorbide were administered orally). It is administered as an intravenous infusion. The main indication for its use is the prevention of acute renal failure; it is effective only if administered early enough, while there is still some diuresis. By ensuring the flow of primary urine through the tubules, this drug prevents necrosis of tubular cells.

Mannitol can also reduce elevated intracranial pressure (e.g., in cerebral edema) and elevated intraocular pressure (in glaucoma). Since mannitol is retained in the extracellular space, it expands it. The result of the expansion of the extracellular space can be **pulmonary edema**. This is the most serious complication of mannitol administration. Due to excessive withdrawal of water from the central nervous system, confusion, visual disturbances, and convulsions may occur.

Finally, recombinant human V-type natriuretic peptide (**nesiritide**) can be used as a diuretic in acute decompensation of congestive heart failure, which, after intravenous administration, leads to natriuresis and increased diuresis. This drug will be discussed in more detail in a separate chapter.

CALCIUM CHANNEL BLOCKERS

Calcium is necessary for the contraction of smooth muscle cells and myocardial cells. Ca++ enters these cells through protein structures in the membrane called calcium channels. The largest number of calcium channels is activated (opened) when the cell membrane is depolarized. That is why we say that they are voltage-gated channels. There are several types of voltage-gated calcium channels: **L** (the most numerous, they got their name from the English word large = wide, big, because after activation they are wide and open for a long time), **T** (the few, they got their name from the English word transient = temporary, because after activation they are open for a short time) and **N** (they are found only on neurons, they got their name from the English word neuronal = neuronal), **P/Q** and **R** (the last two types of calcium channels are also found in nervous tissue). Calcium channel blockers first pass through the cell membrane and then bind to the cytoplasmic side of the channels and block them. There are three binding sites for the blockers, which are indicated by Roman numerals: site I, where 1,4-dihydropyridines bind, site II, where verapamil and similar drugs bind, and site III, where diltiazem binds. Because of the different binding sites, individual calcium channel blockers differ in their mechanism of action and ultimate effects in the body.

The effect of calcium channel blockers is enhanced if the muscle cells are stimulated more often, so this type of blockade is called "**use-dependent blockade**". The reason for this phenomenon lies in the easier binding of these drugs to calcium channels that are either open or inactivated (the state that immediately precedes the closure of the channel).

There are three basic chemical groups of these drugs: 1) **verapamil and its analogues** 2) **1,4-dihydropyridines** (nifedipine, nimodipine, nicardipine, felodipine, amlodipine, nisoldipine, isradipine) 3) **dibenzothiazepines** (diltiazem). Calcium channel blockers act primarily on the heart and smooth muscle of arterial blood vessels. They have depressant effects on the heart: they reduce the conduction velocity in the A-V node, reduce the force of cardiac contraction, reduce excitability and heart rate. On the other hand, they mainly dilate arterial blood vessels and lead to a decrease in blood pressure. Verapamil acts primarily on the heart, and weakly on blood vessels; dihydropyridines primarily dilate arterial blood vessels and have weak effects on the heart. Diltiazem has an equal effect on both the heart and blood vessels. Verapamil is used to treat atrial arrhythmias (it can stop or prevent the onset of paroxysmal supraventricular tachycardia), angina pectoris (exertional angina and vasospastic angina), Raynaud's syndrome (functionally impaired blood flow in the hands and feet), and hypertension. Other calcium channel blockers are used only to treat hypertension, Raynaud's syndrome, and angina pectoris (because by lowering blood pressure they reduce the workload of the heart and myocardial oxygen consumption, and in vasospastic angina pectoris /Prinzmetal's angina/ they also dilate the coronary arteries).

Calcium channel blockers are not used in the treatment of heart failure, because they not only do not improve the patient's condition, but can even worsen it.

Unlike other vasodilators, calcium channel blockers do not cause fluid retention or postural hypotension.

All calcium channel blockers are well absorbed from the gastrointestinal tract. Verapamil and diltiazem are rapidly metabolized in the liver, already during the first pass, but their metabolites are mostly pharmacologically active. On the other hand, nifedipine and other 1,4 - dihydropyridines are metabolized more slowly, to inactive metabolites. Since their half-life is about 5-8 hours, they must be administered 2-3 times a day.

Calcium channel blockers are well tolerated. Mild side effects such as headache, flushing, and swelling of the legs at the level of the malleolus are rare. Verapamil may cause constipation in elderly patients. In principle, calcium channel blockers should not be given together with β-adrenergic receptor blockers. Since both drugs slow conduction through the A-V node in the heart, their simultaneous administration (especially if at least one of them is administered parenterally) may lead to complete A-V block. Also, calcium channel blockers should not be given to people with heart failure because they may worsen it due to a decrease in the force of cardiac contraction. Overdose of calcium channel blockers results in hypotension, bradycardia, and/or A-V block.

When it comes to nifedipine, one should avoid taking doses higher than 20 mg at once, because it causes sudden vasodilation, a drop in blood pressure, and reflex tachycardia; if the patient already has coronary artery disease, myocardial infarction may occur!

Nimodipine and flunarizine stand out in terms of their selectivity. They act mostly on the blood vessels of the brain and cerebellum. That is why nimodipine is used in subarachnoid hemorrhage to prevent the accompanying spasm of these blood vessels, and flunarizine can prevent and suppress migraine attacks. Amlodipine differs from other 1,4-dihydropyridines in that it has a more gradual onset and cessation of action, which facilitates clinical use.

A few years ago, a serious interaction of calcium channel blockers (primarily amlodipine, diltiazem, felodipine, nifedipine and verapamil) with the antibiotic clarithromycin was discovered. If patients on chronic therapy with one of the aforementioned calcium channel blockers are prescribed clarithromycin for an infection, it strongly inhibits cytochrome 3A4 and thus prevents the metabolism of calcium channel blockers, increasing their concentration in the blood by up to five times. The patient then develops severe hypotension, which leads to acute renal failure.

Table 12. Doses of the most important calcium channel blockers.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Nifedipine	Oral	10 mg	8 h
Verapamil	Oral	160 mg	8 h

NITRATES

Nitrates are drugs that have a nitrate group (NO_3) in their molecule. After binding of nitrate to their receptor, the sulfhydryl groups of the receptor reduce nitrate to nitrite and lead to the release of nitric oxide (NO), which activates guanylate cyclase, leading to the accumulation of cyclic guanosine monophosphate and relaxation of smooth muscle cells. Cyclic guanosine monophosphate is thought to cause relaxation by inhibiting the release of calcium from the sarcoplasmic reticulum and inhibiting the entry of calcium into the cell through L-type calcium channels in the cell membrane. Today, the most commonly used nitrates in clinical practice are nitroglycerol, pentaerythritol tetranitrate, isosorbide mono- and di-nitrate.

These drugs relax all smooth muscles, but are used primarily for the dilation of venous blood vessels. Due to this effect, blood accumulates in the veins and thus the flow to the heart is reduced (i.e., the so-called preload of the heart is reduced). The heart now works less and consumes less oxygen. If a patient with narrowed coronary arteries who has had attacks of chest pain (arteriosclerotic angina pectoris) takes nitrates, he will feel an improvement, because due to the reduced needs of the myocardium, the weakened blood flow through the narrowed coronary arteries now becomes sufficient. In vasospastic angina pectoris (Prinzmetal's angina), nitrates help by directly relaxing the coronary arteries. Patients with heart failure will also benefit from taking nitrates. The reduced blood flow to the heart allows the myocardium to work within its capabilities and not be exposed to additional damage due to hypoxia. That is why nitrates are used to treat both angina pectoris and heart failure.

Nitrates are rapidly reduced in the liver to inactive metabolites, so their half-life (and thus their effect) is very short (e.g., half-life of nitroglycerin = 3-8 minutes). To prolong their effect, they are administered either sublingually (nitroglycerin), so that they do not pass through the liver immediately after absorption, or in the form of sustained-release tablets (other nitrates), which release the drug in the intestines over a longer period of time and thus "make up for" the drug that has already been broken down after absorption. Recently, nitroglycerin has been administered transdermally, using a special patch that gradually releases the drug and thus maintains constant concentrations of nitroglycerin in the blood for 24 hours.

After sublingual administration of **nitroglycerin**, the effect begins in 2-5 minutes, and the maximum effect is achieved in about 10 minutes. After 20-30 minutes, the effect is completely lost. When sublingual nitroglycerin is administered, the patient should be in a semi-sitting position, because then the effect will be optimal. Isosorbide dinitrate is metabolized in the liver to two active metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate. **Isosorbide-5-mononitrate** is more resistant to reduction in the liver, so it can also be administered orally. The listed active metabolites, as well as the compounds formed by their further metabolism, are water-soluble and are excreted in the urine.

A special problem with nitrate therapy is the development of **tolerance** to their effect. Tolerance develops rapidly, even during one-day continuous administration. However, since tolerance is lost just as quickly after discontinuation of the drug, intermittent use of nitrates is advised. Namely, they should be used during the day, and not at night; thus, the tolerance created during the day will be lost at night. Intermittent use of nitrates is not without its dangers: early in the morning, before a new dose of nitrate is taken, the concentration of the drug in the blood is practically undetectable, and the patient may experience an attack of angina pectoris, especially if he stands up suddenly or becomes excited. This phenomenon is called the "**zero hour effect**", and the patient's attention should be drawn to it. The side effects of nitrates are mild and are a consequence of their primary effect on the blood vessels. Due to vasodilation of the blood vessels in the neck and head, headache and redness of the face and neck occur, and due to excessive dilation of the veins and excessive reduction of venous inflow to the heart, tachycardia and hypotension may occur. Nitrates **increase intracranial pressure** due to dilation of the veins in the neck and head, so they should not be given to people at risk of brain tissue swelling (injuries, tumors, brain infarction, brain hemorrhage, etc.).

Nitrites act similarly to nitrates, compounds that have a nitrite group (NO_2) in their molecule instead of a nitrate group. The most widely used nitrite is amyl nitrite, a highly volatile substance that was administered by inhalation. Nitrites are rarely used today because, with prolonged use, they lead to significant methemoglobinemia (oxidize Fe^{2+} of hemoglobin to Fe^{3+}), which manifests as pseudocyanosis. Nitrates cause methemoglobinemia much less often, but if administered orally in large doses, part of that dose is converted into nitrites by bacteria in the intestines, which cause methemoglobinemia. Methemoglobinemia can be treated with intravenous infusion of methylene blue (1-2 mg/kg body weight).

Sodium nitrite is used intravenously to induce methemoglobinemia in patients poisoned by cyanide. Methemoglobin binds to the cyanide ion, thus reducing its toxicity.

Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil) are contraindicated in patients receiving nitrate therapy, as severe hypotension, decreased coronary perfusion, and myocardial infarction may occur.

Table 13. Doses of nitrates.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Nitroglycerol	Sublingual	0.5 mg	For aborting angina pectoris attack
	i.v. infusion	10-100 μg/min	-
	Transdermal	15 mg by phlaster	24 h
Pentaerythritol-tetranitrate	Oral	10 mg	6 h
Isosorbide-dinitrate	Oral	10 mg	6 h

ACTIVATORS OF POTASSIUM CHANNELS

Nicorandil is a potassium channel opener, causing dilation of both arteries and veins. It is indicated for the prevention and treatment of chronic stable angina pectoris; its effect is similar to that of other antianginal drugs. It is used in second-line therapy (when beta-blockers and nitrates are no longer effective or cannot be used for some reason), mainly alone, but it can be added to patients already receiving maximum therapy, and then shows an additional beneficial effect. It is also useful for the prevention of acute coronary syndrome in patients with chronic stable angina pectoris who have previously had a myocardial infarction or coronary artery bypass graft surgery.

Due to the risk of excessive hypotension and reduced blood flow to the heart, nicorandil should be dosed with caution. As with nitrates, the concomitant use of nicorandil and phosphodiesterase type 5 inhibitors is contraindicated, as severe hypotension with myocardial hypoperfusion may occur. In recent years, a serious adverse effect of nicorandil has been discovered: it causes ulcerations of the skin (especially the perianal area) and mucous membranes, which sometimes lead to the formation of fistulas. After cessation of nicorandil, the ulcers heal spontaneously. **Pinacidil and cromakalim** also open potassium ion channels, but they have not been developed to the stage of becoming licensed drugs.

BETA BLOCKERS

The sympathetic nervous system exerts most of its stimulatory effect on internal organs through β-receptors. Binding of catecholamines to β-receptors leads to: increased heart rate, increased contractility, faster conduction, and increased cardiac excitability (β1 subtype); bronchodilation (β2 subtype); stimulation of renin release from juxtaglomerular apparatus cells (β1 subtype); increased blood flow through skeletal muscles (β2 subtype); increased insulin release and uterine relaxation (β2 subtype). Blockade of β-receptors in the heart and on juxtaglomerular apparatus cells can achieve very beneficial effects in patients with hypertension, angina pectoris, and arrhythmias. Propranolol, a nonselective blocker of both β1 and β2 receptors, is most commonly used for these indications.

Beta blockers are used to treat hypertension in younger people with healthy myocardium, to treat angina pectoris (because they reduce oxygen consumption), to suppress extrasystoles or paroxysmal tachycardias, and to prevent ischemia in patients who have suffered a myocardial infarction. Propranolol penetrates well into the CNS and stabilizes the membrane potential of neurons there, which has proven to be very useful in the treatment of essential tremor. In principle, they should not be given together with calcium channel blockers because they can lead to conduction block in the heart (A-V block), especially if, for example, verapamil is administered intravenously.

Beta-blockers have a special place in the prevention of recurrent myocardial infarction. If atenolol and metoprolol are started in the acute phase of the infarction, and acebutolol, propranolol and timolol in early convalescence, the possibility of a new heart attack is reduced by half.

Beta-blockers are also used to treat heart failure, because they reduce the hyperactivity of the sympathetic nervous system. Metoprolol, bisoprolol and carvedilol are the most commonly used for this indication.

In addition to all of the above, beta-blockers are useful in the treatment of thyrotoxicosis and in preparing the thyroid gland for surgery. They are also used for the prophylaxis of migraine attacks.

Beta-blockers are moderately absorbed after oral administration. Some of them (propranolol, metoprolol) are metabolized very quickly in the liver, already during the first pass, while the metabolism of others is much slower. Due to moderate absorption and the effect of first-pass metabolism, the bioavailability of most beta-blockers does not exceed 50%. The half-life of most beta-blockers is relatively short (3-6 hours), while for some it reaches 24 hours (e.g. nadolol); therefore, most drugs from this group are administered several times a day.

The side effects of propranolol and other beta-blockers arise from the blockade of β-receptors in other tissues or in the heart itself. Thus, it can lead to bronchoconstriction in asthmatics (blockade of β2 receptors in the bronchi), to worsening of heart failure and conduction block in the heart, to hypoglycemia (in young children, the very elderly and diabetics taking oral antidiabetics), to hypertriglyceridemia and a decrease in HDL-cholesterol, and to a deterioration in the flow through the extremities in patients with atherosclerosis. Due to its penetration into the central nervous system and additional blocking effect on Na+ channels, propranolol can cause nightmares, lethargy and depression. Impotence can also be a problem. These side effects can only be partially overcome by the use of selective β1 antagonists (atenolol, metoprolol, betaxolol, bisoprolol and nebivolol) or by the use of β-blockers that have some stimulatory activity on β-receptors (so-called partial agonists: oxprenolol, pindolol, etc.).

Due to their depressant effect on the myocardium and conduction blockade, β-blockers are contraindicated in patients with 2nd or 3rd degree A-V block.

All beta-blockers show similar clinical efficacy. The choice of drug is made on the basis of differences in additional effects and side effects. Thus, oxprenolol, pindolol, acebutolol and celiprolol also have a sympathomimetic effect, which allows for less bradycardia and better blood flow through the extremities (due to stimulation of beta2 receptors in the blood vessels of the extremities). Atenolol, celiprolol, nadolol and sotalol are more polar substances than other beta-blockers; therefore, they penetrate the CNS less and cause less sleep disturbances and nightmares. Labetalol, celiprolol, carvedilol and nebivolol cause vasodilation, which may be useful in certain clinical situations. Carvedilol is a newer, non-selective beta-blocker that, in addition to beta receptors, also blocks alpha receptors. Due to this additional effect, it does not cause deterioration of blood flow through the extremities, so it can also be used in patients with peripheral arteriosclerosis. Carvedilol also causes less metabolic side effects of beta-blockers. Nebivolol does not cause hypertriglyceridemia and hypoglycemia, but it can mask the signs of hypoglycemia. Bisoprolol is a selective beta 1 blocker that has become very popular among cardiologists in our country in recent years, because it is eliminated in a way that greatly facilitates its use. Bisoprolol has a so-called "balanced elimination", i.e. it is eliminated to a large extent both through the kidneys and through the liver. Therefore, the dose of bisoprolol does not need to be adjusted when the patient has kidney or liver failure.

When using β-blockers, it is very important to know that therapy should not be stopped abruptly! If this is done, the heart suddenly becomes overly sensitive to the effects of the sympathetic nervous system (because the number of β1 receptors has

increased in the meantime, so-called **upregulation of receptors**), which can lead to increased oxygen consumption and angina attacks, or even heart attack. Therefore, long-term use of β-blockers requires their gradual discontinuation, by reducing the dose over a period of several weeks.

Table 14. Doses of some beta-blockers.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Пропранолол	орално	80 mg	12 часова
Метопролол	орално	100 mg	24 часова
Пиндолол	орално	15 mg	12 часова

TREATMENT OF ANGINA PECTORIS

Treatment of angina pectoris and other manifestations of myocardial ischemia is based on two principles: (1) reducing myocardial oxygen demand, and (2) increasing coronary blood flow through the potentially ischemic myocardium. Angina pectoris occurs in three clinical forms, which require specific therapeutic approaches. **Angina on exertion or "classical" angina** pectoris occurs due to morphological narrowing of the coronary arteries (most often due to atherosclerosis), so that increased heart rate and increased oxygen consumption lead to myocardial ischemia. **Vasospastic angina (Prinzmetal's angina)** occurs due to spasm of the coronary arteries, and is usually not associated with physical exertion. **Unstable angina pectoris** occurs due to reversible and recurrent occlusion of the coronary artery by platelets deposited on atherosclerotic plaque, which has ruptured towards the lumen of the blood vessel.

In classical angina pectoris, a large number of clinical studies have shown that beta-blockers, nitrates, calcium channel blockers, ivabradine and drugs that reduce beta-oxidation of fatty acids in the heart prevent and delay the onset of chest pain and ST-segment depression on the ECG during physical exertion. Which drug to choose for the prevention of angina pectoris attacks depends on other patient characteristics. In patients with hypertension, it is most appropriate to use beta-blockers or long-acting calcium channel blockers; in patients with normal blood pressure, it is better to choose retard forms of nitrates. Of course, the termination of classical angina pectoris attacks is best achieved by sublingual administration of nitroglycerin.

Ivabradine blocks ion channels in the cells of the sinoatrial node through which a mixed current of sodium ions and potassium ions passes. The result of its action is a slowdown in heart rate, which saves energy and consumes less oxygen in the myocardium. It is used to prevent attacks of classic angina pectoris alone or in combination with beta blockers. It should not be given to patients with sinus node dysfunction, slow conduction of impulses in the heart or severe heart failure. Side effects of ivabradine are severe bradycardia, ventricular extrasystoles, phosphenes (the appearance of "fireflies" before the eyes), hyperuricemia and an increase in serum creatinine.

Ranolazine and trimetazidine inhibit the enzyme **3-ketoacyl coenzyme A thiolase** in myocardial mitochondria, thereby **reducing beta-oxidation of fatty acids**. Due to this inhibition, myocardial cells are reoriented to glycolysis, so they need less oxygen than usual (because glucose has more oxygen in its molecule than fatty acids). Trimetazidine and ranolazine are as effective as beta-blockers and calcium channel blockers in preventing attacks of stable angina pectoris. They can be used to prevent attacks of angina pectoris alone or in combination with a beta-blocker or calcium channel blocker. Side effects of these drugs include QT prolongation, gastrointestinal complaints, visual disturbances, tinnitus, and mild edema.

In classical angina pectoris, in addition to the aforementioned therapy, patients should be given low doses of acetylsalicylic acid (to prevent the formation of thrombi in the coronary arteries) and cholesterol levels should be lowered by taking one of the statin drugs (see later chapter).

Calcium channel blockers or nitrates can be used both to prevent attacks and to stop attacks of vasospastic angina pectoris. These two groups of drugs can also be combined if the patient does not respond well to monotherapy. The use of beta-blockers in this group of patients does not bring additional benefit.

In unstable angina pectoris, **nitroglycerin and beta-blockers** should be used in the first act; if the patient does not respond favorably to such therapy, **calcium channel blockers** can be added. However, since the basic pathological phenomenon in unstable angina is thrombus formation, antiplatelet (aspirin, ticlopidine or clopidogrel) and anticoagulant drugs (heparin, unfractionated or low molecular weight) should be included in the therapy. The patient must be monitored intensively, so that in the event of complete occlusion, fibrinolytic therapy or emergency percutaneous coronary intervention can be applied.

CARDIOTONIC GLYCOSIDES

Cardiotonic glycosides (digoxin, digitoxin) are natural substances obtained by extraction from foxglove (Digitalis lanata and Digitalis purpurea). English physician William Wiedering was the first to introduce foxglove into official medicine at the end of the 18th century, noticing that a herbalist (whom the locals called a witch) successfully treated heart failure with a mixture of herbs, which included foxglove.

Cardiotonic glycosides block Na+, K+, ATP-ase, the main ion transporter in the membrane of most cells. As a result, a slight depolarization of the membrane occurs, opening channels for the entry of calcium ions and inhibiting the transport of Ca++ out of the cell. The resulting increase in the concentration of calcium ions in the cytoplasm serves as a trigger for increased release of Ca++ from the sarcoplasmic reticulum. Myocardial cells now contract more efficiently: with the same energy expenditure, the contraction has a greater amplitude. This allows the diseased heart to pump blood better, and the symptoms and signs of heart failure subside. At the same time, cardiotonic glycosides increase the activity of the parasympathetic nervous system (especially the vagus nerve), which slows down the conduction of impulses through the A-V node and the atria.

Cardiotonic glycosides are used to treat **heart failure, especially if it is accompanied by atrial fibrillation or flutter**. Unfortunately, although patients experience a visible clinical improvement, cardiotonics **do not affect the length of survival** of these people. Due to the slowing of impulse conduction through the A-V node, cardiotonics are useful for controlling the rhythm of the ventricles in patients with atrial fibrillation or flutter. Digitalis glycosides can also be used to treat isolated atrial arrhythmias: flutter, atrial fibrillation (to restore sinus rhythm) and supraventricular paroxysmal tachycardia. For this last indication (supraventricular tachycardia), a much more effective drug is currently used - adenosine, in the form of an intravenous injection of 6 mg.

Cardiotonics are well absorbed from the gastrointestinal tract. Digoxin is metabolized very little in the liver, and is mainly eliminated unchanged via the kidneys (t1/2 is about 36 hours). Digitoxin, after being metabolized in the liver, is eliminated via the bile (t1/2 is about 7 days). Both drugs can be administered orally and parenterally.

To exert their effect, cardiotonic glycosides must reach a certain concentration in the blood and extracellular fluid. The patient is usually said to be digitalized at this point. The desired therapeutic concentration can be reached in two ways: (1) by so-called gradual (slow) digitalization, when the patient initially receives a maintenance dose (for digoxin, this is 0.25 mg per day, orally), so that the therapeutic concentration is reached after about a week, and (2) by so-called rapid digitalization, when the patient receives a loading dose immediately (for digoxin, this is 0.5 mg i.v. or 0.75 mg orally) and then continues with a maintenance dose (for digoxin, 0.25 mg per day, orally) so that the therapeutic concentration is reached immediately on the same day. Due to the presence of Na+, K+, ATPase in most cells, cardiac glycosides have many undesirable effects. They can be cardiac (A-V block, trough depression of the S-T segment, the appearance of ventricular extrasystoles; often each extrasystole is accompanied by a normal QRS complex in the ECG - such a finding is called **bigeminia**) and extracardiac (nausea, vomiting, seeing a yellow halo around objects, psychosis).

In the event of an overdose of cardiotonics and true poisoning, Fab fragments of antibodies that bind cardiotonics should be administered. The fragments bind to the cardiotonic and thus prevent its harmful effect on cells.

NATRIURETIC PEPTIDES

Natriuretic peptides cause diuresis, natriuresis, and vasodilation. They reduce the secretion of aldosterone and angiotensin 2. The result is a decrease in the workload of the heart; this explains the increased levels of these peptides in the serum of people suffering from heart failure. There are three peptides:

1. **A** (or atrial) natriuretic peptide, secreted by the atria in response to dilation
2. **B** natriuretic peptide, secreted by the ventricles of the heart in response to an increase in pressure at the end of diastole
3. **C** natriuretic peptide, secreted by endothelial cells of blood vessels

Recombinant human B natriuretic peptide (BNP), which has 32 amino acids, is used as a drug, called **nesiritide**. It is indicated for the intravenous treatment of acute heart failure in patients with dyspnea at rest. In these patients, nesiritide improves dyspnea and reduces pulmonary capillary wedge pressure. Nesiritide must be dosed with caution to avoid excessive hypotension, which may worsen the patient's condition. Therefore, its use is contraindicated in patients with a systolic blood pressure below 90 mmHg. In

patients whose renal function depends on the formation of angiotensin II and the release of aldosterone, nesiritide may cause an increase in serum creatinine and urea.

Nesiritide is given as an intravenous injection of 2 μg/kg, followed by an infusion of 0.01 μg/kg/min. It is eliminated from the circulation by the action of endopeptidases and renal filtration. The half-life is 18 minutes.

A modified recombinant natriuretic peptide C, called **vosoritide**, is used to treat achondroplasia in children whose epiphyses have not yet closed. It binds to the type B receptor for natriuretic peptides and reduces the activity of the fibroblast growth factor receptor, which normally inhibits bone and cartilage growth. As a result of this action of vosoritide, cartilage formation is restored.

TREATMENT OF HEART FAILURE

The goal of heart failure treatment is not only to reduce symptoms and improve heart function, but also to reduce mortality. Digoxin has long been the cornerstone of heart failure treatment, but its place has now been taken by ACE inhibitors; the reason for this is the fact that ACE inhibitors, in addition to improving the clinical picture, also reduce mortality, which is not the case with digoxin.

ACE inhibitors are used in the treatment of heart failure in high doses, even higher than those with which they are registered. Angiotensin 2 receptor blockers (valsartan, telmisartan), which achieve the same effect, can be used instead of ACE inhibitors. Diuretics, such as thiazides (if kidney function is normal) or loop diuretics (if kidney function is impaired), are often used in combination with ACE inhibitors or angiotensin II receptor blockers. In more severe cases, it is even possible to combine both types of diuretics, or to add spironolactone, which has been shown to further reduce mortality. Continuous monitoring of serum creatinine and potassium is necessary.

In recent years, a combination of **valsartan and sacubitril** has been used with success in the treatment of heart failure, especially when the ejection fraction is reduced and symptoms are present (valsartan is an angiotensin II receptor blocker, and sacubitril is a prodrug whose metabolite blocks the enzyme **neprilysin**, which normally degrades natriuretic peptide).

The β-blockers bisoprolol, carvedilol, and metoprolol can be used to treat stable heart failure, especially left ventricular dysfunction. Their use begins with very low doses, which are carefully increased to the optimal effect.

The antidiabetic drugs **empagliflozin and dapagliflozin** are also used in the treatment of heart failure with preserved ejection fraction. These drugs selectively inhibit the SGLT2 glucose transporter, which reabsorbs glucose from the lumen of the renal tubules, which is the basis of their positive effect in diabetes. However, dapagliflozin and empagliflozin also inhibit sodium reabsorption in the renal tubules, which **reduces the body's sodium load**, and thus the preload and afterload on the heart. The main side effect of these drugs is an increased incidence of urinary tract infections.

Digoxin is currently used only in patients with heart failure and atrial fibrillation, or in patients who do not respond favorably to other therapy.

Calcium channel blockers should never be used in patients with heart failure, as they can worsen it and increase the risk of death.

When a patient is in **acute heart failure, milrinone** can be used, a drug that specifically blocks phosphodiesterases in the heart, leading to the accumulation of cAMP and an increase in the concentration of calcium in the cytoplasm. All of the above changes result in increased myocardial contractility and better relaxation of the heart chambers in diastole. Milrinone also causes vasodilation in the pulmonary circulation, but also systemically, which further facilitates the work of the heart. It is administered parenterally, as well as i.v. infusion. The main danger with the use of milrinone is the possibility of induction of ventricular arrhythmias, so strict monitoring of the ECG and ion concentrations in serum is necessary.

In addition to milrinone, acute heart failure can be treated with **dobutamine**, as an intravenous infusion, which stimulates beta 1 receptors in the heart, as well as **levosimendan**, a drug that sensitizes troponin C to calcium, so that myocardial contraction is more efficient with the same energy expenditure. In addition to this effect, levosimendan opens potassium channels and leads to vasodilation and sparing of the myocardium. Compared to milrinone and dobutamine, levosimendan is equally effective, and has fewer side effects, which are generally mild (hypotension, hypokalemia, tachycardia and rarely atrial fibrillation).

TREATMENT OF MYOCARDIAL INFARCTION

Initial treatment of myocardial infarction is carried out with the use of oxygen, morphine (for pain relief), aspirin (300 mg, for its antiplatelet effect) and a thrombolytic drug (must be added within 12 hours of the onset of the infarction, ideally within the first 60 minutes). Heparin is administered in addition to the thrombolytic drug to prevent re-thrombosis. Nitrates (to reduce pain),

beta-blockers (atenolol, metoprolol) and ACE inhibitors are also used (should be started within the first 24 hours of the infarction, provided that the blood pressure is normal; the administration is then continued for 6 weeks).

In the continuation of the treatment of the infarction, aspirin (75 mg/day), a beta-blocker (acebutolol, metoprolol, timolol or propranolol if there is no left ventricular failure, and carvedilol, bisoprolol or metoprolol if there is left ventricular failure), an ACE inhibitor (if there is left ventricular failure), nitrates (if there is angina pectoris) and a statin (to prevent myocardial infarction) are prescribed. Today, an increasing number of patients with acute myocardial infarction undergo emergency percutaneous interventions on the coronary arteries, which first involve coronary angiography to locate the site of narrowing of the arteries, followed by balloon dilation of that site and insertion of a coronary stent (a metal tube with a mesh wall) that prevents the coronary artery from narrowing again. These interventions mechanically resolve the issue of ischemia, so the therapy is focused on the use of antiplatelet drugs that should prevent thrombosis and stent occlusion. If the patient was not taking an oral antiplatelet drug from the P_2Y_{12} inhibitor group before the intervention, the patient is given **cangrelor**, a direct inhibitor of the P2Y12 receptor, intravenously during the intervention. After the intervention, the patient is given **dual antiplatelet therapy** orally (**aspirin + another antiplatelet drug**). This dual therapy must last at least 6 months if the stent is ordinary, metallic, and at least a year if the stent is metallic, but also designed to release drugs from the immunosuppressive group (which prevent endothelial proliferation and stent occlusion in another way).

ANTIARRHYTHMICS

Arrhythmias are disturbances in the normal, sinus rhythm of the heart (about 70-80 beats per minute, with equal intervals between beats). The disturbed rhythm of the heart can be too slow, too fast, or with unequal time intervals between beats. Types of arrhythmias are: bradycardia, heart block, extrasystoles, tachycardia, flutter and fibrillation. Depending on the localization, they can be atrial or ventricular arrhythmias.

Arrhythmias can occur for two reasons: (1) due to disturbances in the generation of impulses, or (2) due to disturbances in the conduction of impulses. Arrhythmias due to disturbances in the generation of impulses occur due to premature depolarization of the cells that determine the rhythm of the heart, i.e. "pacemaker" cells. In addition to the cells of the conduction system, any other heart cell can, under certain conditions (hypokalemia, acidosis, ischemia), acquire the characteristics of cells that spontaneously depolarize. Then the cell with the fastest spontaneous depolarization becomes the abnormal leader of the heart rhythm, i.e., the focus of the arrhythmia.

A special cause of arrhythmia due to disturbances in the generation of impulses is the occurrence of early and late after-depolarizations (early ones occur before the repolarization of the heart cell has occurred, and late ones only after full repolarization has occurred). Late after-depolarizations are a consequence of an increased concentration of calcium inside the cell, e.g. with prolonged use of cardiotonic glycosides.

Arrhythmias due to disturbances in the conduction of impulses involve the occurrence of a block in the conduction of impulses; The block can be complete (bidirectional), when impulses cannot spread further, or unidirectional, when impulses in a part of the heart tissue cannot spread in one direction, but can in the opposite direction, and very slowly. When there is a bidirectional block, arrhythmias known as SA block, AV block or bundle branch block occur. When there is a unidirectional block, the depolarization wave spreads through normal tissue, while it quickly dies out in the blocked tissue. However, when the depolarization wave bypasses the blocked site, it begins to spread through it on the other side, in the opposite direction. If the propagation of the depolarization wave in the opposite direction is slow enough, upon leaving the site of the blockage, it will find healthy myocardium capable of depolarizing again. Then a premature impulse occurs, i.e. extrasystole. The whole cycle is then repeated, in order to produce a new extrasystole, i.e. tachycardia is established. This mechanism of arrhythmia formation is called the "**re-entry phenomenon**".

Antiarrhythmics are drugs that prevent and treat arrhythmias. They affect the ion channels that participate in the processes of depolarization and repolarization of heart cells, mainly by blocking them. Since antiarrhythmics primarily bind to channels that open more frequently, they will have a stronger effect on the parts of the myocardium that are generators of arrhythmias.

According to the mechanism of action, antiarrhythmics can be divided into 4 groups.

The first group includes drugs that block sodium ion channels and thus make it more difficult for depolarization to occur (they are said to "stabilize" the membrane). Although they act on Na+ channels in all parts of the heart, they block the channels much more strongly in parts of the heart that depolarize more often and more easily - these are the parts of the heart affected by the pathological process (this is the so-called "use-dependent blockade") and parts of the conduction system (the bundle of His and Purkinje fibers). Depending on how they affect the length of the action potential, they are divided into 3 subgroups:

• Ia - drugs that prolong the action potential and the refractory period (during which cells cannot depolarize again) - quinidine, procaineamide, disopyramide and moricizine. They slow down phase 0, slow down spontaneous depolarization in phase 4 and slow down conduction in the heart.

• Ib - drugs that shorten the action potential and the refractory period - lidocaine, mexiletine, tocainide and phenytoin.

• Ic - drugs that do not affect the length of the action potential and the refractory period - encainide, flecainide and propafenone.

Group Ia drugs are very effective, but have many side effects. All have negative inotropic effects and can cause arrhythmias if dosed inadequately. Quinidine has pronounced central side effects (ringing in the ears, dizziness and a state similar to drunkenness), is toxic to the bone marrow and can cause a characteristic ventricular tachycardia that appears on the ECG as a series of spikes - French: "torsade de pointes"). **Procainamide** can cause a syndrome similar to systemic lupus erythematosus in people who slowly break down this drug (so-called slow acetylators). **Disopyramide** has pronounced antimuscarinic side effects (dry mouth, constipation, urinary retention, etc.). Quinidine is an alkaloid from the Cinchona plant (China tree), which grows in tropical regions. It is an optical isomer of quinine, which deflects polarized light to the right. Like quinine, quinidine has antiarrhythmic, antimalarial, antipyretic, and muscle relaxant effects. It can also stimulate contractions of the gravid uterus, and exhibits anticholinergic effects. The ECG of a patient receiving quinidine may show prolongation of the PR, QRS, and QT intervals. Due to its negative inotropic and vasodilator effects, quinidine causes hypotension.

Quinidine is used to suppress extrasystoles in all parts of the heart, to establish sinus rhythm in patients with atrial fibrillation or flutter (but only if the patient has previously received digoxin, which controls the number of impulses passing from the atria to the ventricles through the AV node; due to its anticholinergic effect, quinidine could increase AV node permeability and lead to dangerous ventricular tachycardia), to maintain sinus rhythm after electrical conversion of atrial fibrillation or flutter to sinus rhythm, to terminate ventricular tachycardia, and to suppress tachycardia attacks in Wolff-Parkinson-White syndrome.

The most common side effects of quinidine are diarrhea and dyspepsia (occurring in more than a third of patients), dizziness (15%), headache, and fatigue. In the heart, quinidine can cause conduction block or provoke ventricular arrhythmias. Thrombocytopenia may occur in a small number of patients. High doses of quinidine can lead to the appearance of the "cinchonism" syndrome, which consists of the following symptoms: ringing in the ears, headache, nausea, blurred vision, dizziness, confusion. Extremely high doses of quinidine lead the patient to delirium with hallucinations.

Quinidine increases the concentration of digoxin in the serum, so the dose of digoxin must be reduced to avoid its toxic effects.

Procainamide acts directly on the myocardium in a manner very similar to quinidine. It is a derivative of the local anesthetic procaine, which, in addition to its antiarrhythmic properties, also has a negative inotropic and hypotensive effect. Due to its short duration of action, which requires frequent administration of the drug, procainamide is used in patients who cannot tolerate quinidine or have not responded well to it.

Adverse effects of procainamide include conduction block in the heart, the development of ventricular arrhythmias, confusional state (rare), agranulocytosis (rare), and a systemic lupus-like syndrome (in about 30% of patients).

Disopyramide acts directly on the myocardium in the same way as quinidine and procainamide. In addition, it has a strong anticholinergic effect. Like quinidine and procainamide, disopyramide has a negative inotropic effect on the myocardium, but does not cause hypotension. It is used to suppress ventricular extrasystoles and tachycardia.

Side effects of disopyramide are impulse conduction disorders, arrhythmias (especially in people with congenital prolongation of the QT interval), heart failure, anticholinergic effects and hallucinations (rarely).

Moricizine exhibits effects on the myocardium that are common to groups Ia and Ib. It inhibits sodium channels in such a way that the blockade is more pronounced at a higher frequency of depolarization. It has no hemodynamic effects and does not prolong the QT interval. It is used to suppress ventricular tachycardia. It is not used in patients with myocardial infarction, as it increases mortality.

Group Ib drugs are the safest to use than group I antiarrhythmics (they do not have a negative inotropic effect on the myocardium), but if overdosed, they can cause excitation of the central nervous system (confusion, convulsions) and arrhythmia.

Lidocaine, through the blockade of sodium channels, leads to a decrease in the amplitude of the action potential and a decrease in the reactivity of the myocardial cell membrane. It does not affect the speed of impulse conduction through the AV node. A shortening of the QT interval can be observed on the ECG. Lidocaine is indicated for the suppression of ventricular arrhythmias in patients with myocardial infarction, as well as for the treatment of arrhythmias in intoxication with cardiotonic glycosides.

Due to its low bioavailability after oral administration (30%), lidocaine is administered only parenterally. Its effect lasts for a short time (10-20 minutes after intravenous administration) because it is rapidly degraded in the liver.

Lidocaine causes drowsiness in most patients, while some experience paresthesias, disorientation, psychosis, and convulsions. It rarely causes hypotension at recommended doses.

Phenytoin has the same effects on the myocardium as lidocaine. It causes transient hypotension and has a negative inotropic effect. Phenytoin is used to treat ventricular arrhythmias after myocardial infarction, anesthesia, cardiac catheterization, and with concomitant use of cardiotonic glycosides (here it is particularly effective, as it eliminates the depressive effect of digoxin on conduction in the AV node). It should not be given to patients with atrial fibrillation or flutter, as it may accelerate conduction of impulses to the ventricles.

Tocainide is chemically similar to lidocaine. Its effects on the myocardium are similar to those of lidocaine. It is administered orally in the treatment of symptomatic ventricular arrhythmias that have not responded to other antiarrhythmics.

In about 15% of patients, the drug causes dizziness or nausea. Paresthesia and tremor are also relatively common. Serious side effects, such as thrombocytopenia, agranulocytosis, or pulmonary fibrosis, can occur very rarely.

Mexiletine acts very similarly to lidocaine and tocainide. It is administered orally in the treatment of ventricular arrhythmias. It is beneficial in people with congenital QT prolongation. Side effects of mexiletine include hypotension, dyspepsia, tremor, dizziness, and impaired coordination.

Group Ic drugs are rarely used today, because in a small (but significant) number of patients they cause fatal arrhythmias.

Flecainide blocks sodium channels and slows conduction in all parts of the heart, especially in the bundle of His and Purkinje fibers. The ECG shows prolongation of the PR interval, QRS complex, and QT interval. Flecainide also has a negative inotropic effect. It is used to treat both ventricular and atrial arrhythmias. Along with digoxin, flecainide is the only antiarrhythmic used to treat fetal arrhythmias.

Side effects of flecainide include: dizziness, visual disturbances, headache, worsening of heart failure, and arrhythmias.

Propafenone acts directly on the myocardium like flecainide, but has an additional blocking effect on beta receptors and calcium channels. In the atria, propafenone prolongs the action potential and refractory period, and in the AV node and ventricles it only slows down conduction. It also slows down the work of the sinus node. The ECG shows a prolongation of the PR interval and QRS complex. It is used to treat both atrial and ventricular arrhythmias, but only if there are no morphological changes in the myocardium. In patients with morphological changes, propafenone increases mortality due to its pro-arrhythmic effect.

In one third of patients, propafenone causes nausea and dizziness.

Group II antiarrhythmics include beta-blockers (propranolol, acebutolol, esmolol, etc.) that reduce the arrhythmogenic effect of the sympathetic nervous system on the heart.

In addition to blocking beta-receptors, **propranolol** acts directly on the myocardium, similar to quinidine. It slows down the sinus node and conduction in the AV node, atria and ventricles. The ECG can show a prolongation of the PR interval. Propranolol is used to treat atrial and ventricular arrhythmias that are a consequence of excessive sympathetic activation (after myocardial infarction, during the use of general anesthetics, etc.). Together with digoxin or alone, propranolol is also used to control the frequency of ventricular work in patients with atrial flutter or fibrillation. It is also the drug of choice for patients with congenital prolongation of the QT interval.

Esmolol is a selective beta1-blocker, which acts for only about 20 minutes, due to its rapid breakdown in plasma, under the action of esterase enzymes. It is administered intravenously for rapid control of ventricular rate in patients with atrial flutter or fibrillation.

Group III includes drugs that prolong the action potential and refractory period, most likely by blocking K+ channels. These are bretylium, sotalol, dofetilide and ibutilide. Sotalol also blocks beta-receptors. By prolonging the action potential, the refractory period is also prolonged, so that the re-entry mechanism is interrupted. Drugs from this group, like all other antiarrhythmics, can sometimes cause arrhythmias themselves.

Bretylium is a very effective antiarrhythmic that increases the threshold for the onset of ventricular fibrillation. It also initially (1-2 hours) increases the release of noradrenaline from sympathetic neurons, and then leads to a decrease in their activity. Bretylium is used to treat the most severe ventricular arrhythmias and facilitates the establishment of sinus rhythm after defibrillation. It is administered intravenously.

The most important side effect of bretylium is hypotension, which occurs due to the blockade of adrenergic neurons. It also causes nausea, vomiting, and swelling of the parotid glands.

Sotalol, in addition to its direct effect on the myocardium, blocks beta-receptors. It prolongs the duration of the action potential and the refractory period. It reduces systolic pressure and stroke volume. It is used to treat both ventricular and atrial arrhythmias. Sotalol is administered orally.

Sotalol can cause ventricular arrhythmias, especially in people with a prolonged QT interval. It can also cause side effects characteristic of beta-blockers.

Dofetilide selectively inhibits the fast component of the delayed potassium current, which contributes to repolarization. It does not affect conduction through the AV node, and in other parts of the myocardium it prolongs the action potential and the refractory period. An extension of the QT interval can be observed on the ECG. The drug is well absorbed after oral administration. Dofetilide is used to treat atrial fibrillation and flutter.

The biggest problem with the use of dofetilide is the possibility of developing a ventricular arrhythmia called "torsade de pointes", due to prolongation of the QT interval. This dangerous arrhythmia occurs in about 3% of patients, most often in the first days of therapy.

Ibutilide is very similar to dofetilide. The only difference is that it is rapidly broken down in the liver, so it must be administered parenterally. It is used for the chemical conversion of atrial fibrillation and flutter to sinus rhythm.

Group IV antiarrhythmics include calcium channel blockers (verapamil and diltiazem). Verapamil blocks the entry of calcium ions through L-type channels into cardiac myocytes. This slows down the spontaneous depolarization of SA node cells and slows down conduction through the AV node. Verapamil is used to treat atrial arrhythmias and to slow down the ventricular rate in the presence of atrial fibrillation or flutter.

A special antiarrhythmic is **amiodarone.** It is a drug that binds tightly to many tissues and is eliminated very slowly from the body (t1/2 is about 100 days). It is metabolized in the liver to active metabolites, which are excreted in the bile. It acts in several ways: by blocking Na+ and K+ channels, by blocking beta-receptors and by blocking calcium channels. It prolongs the action potential and refractory period in all parts of the myocardium. It reduces oxygen consumption in the heart and causes significant hypotension after intravenous administration.

Amiodarone is the most effective of all antiarrhythmics, and has a very low tendency to cause ventricular arrhythmias of the torsades de pointes type. It is used in all types of arrhythmias, especially in the most severe ventricular ones. Unfortunately, the drug has pronounced extracardiac toxicity. It can cause hypothyroidism (due to the iodine it contains), corneal clouding, dark skin discoloration, hair loss, photosensitivity, tremor, nightmares, peripheral neuropathy, pulmonary fibrosis, and liver damage.

A benzofuran derivative of amiodarone is called **dronedarone,** and it is used to maintain sinus rhythm in patients who previously had atrial fibrillation, so conversion to sinus rhythm was performed. Like amiodarone, dronedarone acts in several ways: by blocking Na+ and K+ channels, by blocking beta-receptors, and by blocking calcium channels. Dronedarone should not be given to people who have or have had heart failure, as it may worsen or provoke it. It is less toxic than amiodarone, but it can still cause pulmonary fibrosis in a small number of patients.

Adenosine also occupies a special place among antiarrhythmics. By acting on its receptors, which are found only in the atria and AV node, adenosine opens potassium channels and thereby reduces the rate of spontaneous depolarization. In the AV node, adenosine slows down conduction. As an intravenous bolus injection, adenosine interrupts atrial and nodal (from the AV node) tachycardias. Its action lasts only 15 seconds, as it is rapidly broken down in erythrocytes.

Adenosine causes a brief increase in blood pressure, followed by hypotension. Facial flushing and bronchospasm occur. It should not be given to people with AV block.

Contraindications for the use of antiarrhythmics. If there are disturbances in the conduction of impulses in the heart (AV block, sick sinus syndrome, etc.), the use of antiarrhythmics is contraindicated because these disturbances worsen.

Table 15. Doses of the most commonly used antiarrhythmics.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Procainamide	oral	500 mg	4 h
Quinidine	oral	200 mg	6 h
Lidocaine	i.v.	50 mg bolus i.v. injection, then 20 μg/kg/min i.v. infusion	
Mexiletine	oral	300 mg	8 h
Amiodarone	oral	600 mg	24 h
Propranolol	oral	20 mg	6 h

Bretilium	i.v.	5 mg /kg bolus	1 mg/min i.v. infusion
Verapamil	i.v.	0.1 mg /kg	After 30 minutes it can be repeated

TREATMENT OF ARRHYTHMIAS

Екстрасистоле се лече само ако постоји морфолошко оштећење миокарда; тада је најбоље користити β-блокаторе.

Пароксизмална суправентрикуларна тахикардија се може сузбити стимулацијом вагуса (нпр. Валсалвиним манев-ром). Ако то не успе, може се прекинути и.в. применом вера-памила; то је посебно индиковано код болесника без обољења миокарда или валвула. Друга могућност је интравенска при-мена аденозина. Аденозин има предност над верапамилом у томе што се може применити и у ситуацији где је болесник претходно примао β-блокаторе.

Атријална фибрилација и флатер. Док је код флатера терапијски циљ поновно успостављање синусног ритма, код фибрилације се тежи само контроли броја импулса који у јединици времена пролазе у коморе.

Флатер се може претворити у синусни ритам електро-шоком или употребом амјодарона или дофетилида. У оба случаја, неколико месеци пре конверзије пацијента треба по-двргнути антикоагулантној терапији, како би се спречила могућност настанка емболије.

Учесталост рада комора срца код атријалне фибрилације се може контролисати β-блокатором или верапамилом код особа без срчане инсуфицијенције, док је примена дигоксина исплативија код особа са срчаном инсуфицијенцијом. Код ста-рих особа са атријалном фибрилацијом, или код оних са обо-љењима залистака или миокарда, индикована је примена орал-них антикоагуланаса, како би се спречио настанак тромба у преткоморама, а затим и емболија.

Коморска тахикардија се акутно лечи лидокаином, а када се стање стабилизује примењују се остали антиаритмици I групе или амјодарон.

Посебан ентитет представља коморска тахикардија *torsade de pointes*, коју изазивају лекови који продужавају QT интервал. Ова аритмија се прекида интравенском применом магнезијум сулфата (8 mmol Mg^{2+} током 10-15 минута).

DRUGS FOR HYPERLIPIDEMIAS

After the absorption of triglycerides and cholesterol from food, chylomicrons are formed in the epithelial cells of the small intestine - complex particles whose middle consists of triglycerides and cholesterol and the surface of phospholipids and proteins. Chylomicrons reach the venous blood through the lymph flow, and then to the peripheral tissues (fat and muscle), where they are broken down by the enzyme lipoprotein lipase, bound to the membrane of endothelial cells. The rest of the chylomicrons are converted via IDL lipoproteins (intermediate-density lipoproteins) into LDL lipoproteins (low-density lipoproteins) that contain a lot of cholesterol. Normally, LDL bind to their receptors on hepatocytes and are taken up by liver cells. In the case of excess LDL (e.g., with an excessive diet full of cholesterol), they are also taken up by the cells of the intima of blood vessels. Excessive accumulation of LDL in these cells leads to their transformation into foam cells and, ultimately, to their death and the formation of plaque. In the period between meals, the liver produces VLDL (very low density lipoproteins) that contain triglycerides and cholesterol. VLDL go to peripheral tissues, which, after degradation by lipoprotein lipase, supply fatty acids and glycerol. The rest of the VLDL is converted to LDL via IDL.

Hyperlipidemias can be congenital and acquired. Congenital hyperlipidemias can predominantly have elevated cholesterol or triglycerides. Normally, the level of triglycerides in the serum should be less than 2.5 mM/l, and the level of cholesterol below 4.4 mM/l.

The first step in the treatment of hyperlipidemia is diet. The patient must reduce fat intake to below 20% of the total caloric value of the meal, and cholesterol in particular to below 200 mg/day. After 3 months, the dietitian should re-measure the concentration of lipoproteins (or at least triglycerides and cholesterol) and, if they are elevated, drug therapy should be applied.

Hypertriglyceridemias (hyperlipidemias in which triglycerides predominate) are treated with **fibric acid derivatives (fenofibrate, gemfibrozil, clofibrate)**. These drugs activate a nuclear receptor called the "peroxisome proliferator-activated receptor" (PPAR), which increases the transcription of the lipoprotein lipase gene and decreases the transcription of the apolipoprotein C3 gene (which otherwise inhibits lipoprotein lipase). This increases the activity of lipoprotein lipase and promotes the removal of triglycerides from the circulation. In addition to this effect, fibrates increase the level of HDL particles, because they increase the synthesis of their apolipoprotein A1.

Fibrates are used to treat congenital hyperlipidemias, in which triglycerides are elevated: familial hypertriglyceridemias (type 4) and dysbetalipoproteinemias (type 3). In dysbetalipoproteinemia, fibrates must be used together with a cholesterol-lowering drug, e.g. nicotinic acid. Fibrates also have a beneficial effect on secondary hyperlipidemia, which occurs in patients with type 2 diabetes.

Unfortunately, fibric acid derivatives have a number of serious side effects that limit their use (increased incidence of gallstones, myositis, hepatitis, erectile dysfunction, nausea). In addition, they increase the concentration of LDL, a lipoprotein that promotes the development of atherosclerosis.

Fibrates should not be given together with statins, as the risk of myositis increases. Fibrates also potentiate the anticoagulant effect of warfarin.

An alternative drug for the treatment of hypertriglyceridemia is **nicotinic acid (niacin).** It reduces the production of VLDL lipoproteins in the liver, promotes the uptake of LDL lipoproteins in the liver, and reduces the release of fatty acids from adipose tissue. All of this leads to a decrease in both triglycerides and cholesterol in the blood. The level of HDL particles in the plasma also increases. Therefore, nicotinic acid, in addition to the treatment of hypertriglyceridemia, is also used for the treatment of hypercholesterolemia. It is used alone for the treatment of type 4 hypertriglyceridemia, in combination with statins for the treatment of type 2b hyperlipidemia, and in combination with fibrates for the treatment of dysbetalipoproteinemia (type 3).

Nicotinic acid leads to the release of prostaglandins and a flu-like syndrome. Taking an aspirin tablet 30 minutes before nicotinic acid, and taking the drug with food, can prevent this syndrome. After prolonged use, hepatitis, hyperglycemia, and hyperuricemia occur.

Hypercholesterolemia can also be treated with **anion exchange resins (cholestyramine or colestipol)**, which are taken orally, are not absorbed in the digestive tract, and bind (with ionic bonds) bile acids. This increases the excretion of bile acids through the feces, and reduces the amount of bile acids that, after reabsorption in the ileum, reach the liver again. The liver intensifies the production of bile acids from cholesterol, so LDL particles are taken up from the blood more intensively because the number of LDL receptors on hepatocytes increases. Since they are not absorbed, these drugs, except for bloating and sometimes constipation, do not have any significant side effects. Only in small children, due to the release of chlorine ions from the resins due to the binding of bile salts, can hyperchloremic acidosis occur. Since they are taken in large quantities (about 20 grams per day) and have an unpleasant taste, they are usually administered mixed with fruit juice.

Resins are used to treat hyperlipoproteinemia type 2a, where they can lower LDL cholesterol levels by 25%. Resins in the lumen of the gastrointestinal tract can bind a large number of drugs to themselves, thus interfering with their absorption. Therefore, other drugs are not administered one hour before and 4-6 hours after taking resins.

A new group of drugs, very effective in the treatment of hypercholesterolemia, are **hydroxymethyl-glutaryl-CoA reductase inhibitors** (HMG-reductase, an enzyme that catalyzes a key reaction in cholesterol synthesis, the conversion of hydroxymethyl-glutaryl to mevalonate). They reduce cholesterol synthesis in the liver, so LDL particles from the blood are taken up by the liver more intensively, due to the increased number of LDL receptors on hepatocytes. **Lovastatin, simvastatin, atorvastatin, fluvastatin** and others from this group (collectively called statins) significantly reduce the level of cholesterol and LDL in the circulation.

In addition to the aforementioned effect, statins reduce the synthesis of isoprene geranylgeranyl and farnesyl. This reduces the binding of isoprene to numerous plasma proteins (isoprenylation), and prevents their proliferative effect on smooth muscle cells in the arterial wall.

Statins are used to treat familial hypercholesterolemia type 2a, as well as for the treatment of acquired hypercholesterolemia. In addition, they are used in people who have had a myocardial infarction, regardless of cholesterol levels, because they have been shown to reduce the frequency of recurrent infarction. Such use is called secondary prevention.

The problem with their use is their side effects: rare but serious rhabdomyolysis and chemical hepatitis. The patient should be warned to contact a doctor at the first appearance of muscle pain, in order to prevent the development of extensive rhabdomyolysis, with the release of myoglobin and obstruction of the renal tubules (i.e. with the development of acute renal failure). The simultaneous use of statins and fibric acid derivatives should be avoided, because the risk of rhabdomyolysis increases.

Lovastatin, simvastatin and atorvastatin are metabolised in the liver by cytochrome P450 3A4, and fluvastatin by isoform 2C9. Drugs and foods that inhibit cytochrome 3A4 slow down the metabolism of statins and increase their concentration in the blood by 8-10 times. These are: itraconazole, erythromycin, cyclosporine and grapefruit juice. Conversely, drugs that stimulate the activity of cytochrome 3A4 (phenobarbitone, carbamazepine, rifampicin) accelerate the metabolism of statins and reduce their concentration in the blood. Since warfarin is metabolised, like fluvastatin, by cytochrome 2C9, these two drugs interfere with each other's elimination and increase their concentration in the blood.

Another mechanism of action has an even more effective drug for lowering blood cholesterol levels – the monoclonal antibody **evolocumab**. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is the ninth member of the "proprotein convertase" family of proteins that activate other proteins. PCSK9 binds to the LDL receptor on liver cells and leads to their internalization and destruction. Evolocumab is a human monoclonal antibody that blocks PCSK9 in the bloodstream, thereby preventing the breakdown of LDL receptors. The result is an increase in the number of receptors and greater uptake of cholesterol from the bloodstream, i.e. a decrease in blood cholesterol levels. Evolocumab is administered subcutaneously, once a month, and reduces blood cholesterol levels by as much as 75% (the maximum effect of statins is about 45%). The main side effects of evolocumab are arthralgia and an increased frequency of various infections. Another way to reduce the destructive effect of PCSK9 on LDL receptors is to inhibit its synthesis. The new drug **inclisiran** is a double-stranded RNA that interferes with the synthesis of PCSK9, and thus ultimately increases the number of LDL receptors. Incisiran is administered for 6 months, as a subcutaneous injection, which is enough to reduce LDL cholesterol in serum by 50%. The drug is well tolerated, and no serious side effects have been recorded so far.

A special group of drugs are substances that prevent the absorption of fats. The first drug to appear in this group is **orlistat,** an inhibitor of pancreatic lipase. By preventing the breakdown of triglycerides in the intestines, it also prevents their absorption; thus, triglycerides reach the colon, giving fatty stools. Although orlistat has shown some efficacy in the treatment of obesity (annual weight loss is 4 kg greater with both orlistat and diet compared to diet alone), it has no clinically significant effect on serum cholesterol and triglyceride levels.

A useful addition to statin therapy is the drug **ezetimibe**, which selectively inhibits the absorption of cholesterol and similar phytosterols. It successfully reduces the level of cholesterol, LDL lipoproteins and apolipoprotein B in patients with primary hypercholesterolemia. It is always used in combination with HMG-CoA reductase inhibitors, because it is not effective enough on its own. The drug is administered once a day, orally, at a dose of 10 mg. Side effects are mild: fatigue, diarrhea, abdominal pain, joint and back pain, cough.

The newest drug for the treatment of homozygous familial hypercholesterolemia **is lomitapide**, which selectively inhibits the microsomal transfer protein in the lumen of the endoplasmic reticulum. The role of this protein is crucial in the formation of lipoproteins containing apolipoprotein B (chylomicrons, VLDL, LDL and IDL), so after the administration of this drug, the secretion of chylomicrons from the intestine and VLDL lipoproteins from the liver into the bloodstream is reduced. Lomitapide reduces the level of cholesterol and triglycerides in the blood by about 40%. The drug is taken orally. It is well absorbed from the intestine, but is metabolized in the liver by cytochrome P450 3A4 during the first pass, so its bioavailability after oral administration is only 7%. It is liposoluble, and penetrates all tissues. It can increase the level of aminotransferases in serum.

Mipomersen is an antisense oligonucleotide (20 nucleotide bases) that binds to the transfer RNA encoding apolipoprotein B. The resulting complex is degraded by an RNAase, resulting in less apolipoprotein B formation and therefore less chylomicrons and VLDL secretion into the bloodstream. The drug is administered subcutaneously or intravenously, once every 3 weeks. Mipomersen is approved for the treatment of homozygous familial hypercholesterolemia, where it lowers triglyceride and cholesterol levels by about 30%. Among the side effects, it causes a flu-like condition after injection, and may increase the level of aminotransferases in serum.

Table 16. Doses of hypolipemics

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Nicotinic acid	oral	500 mg	8 h
Gemfibrozil	oral	600 mg	12 h
Atorvastatin	oral	20 mg	12 h

PHARMACOLOGY OF HORMONES

HYPOTHALAMIC AND PITUITARY HORMONES

The hypothalamus secretes substances that control the release of hormones from the anterior pituitary.

A 10-amino acid polypeptide secreted in the hypothalamus reaches the pituitary gland via the portal system, where it causes the release of the gonadotropic hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This polypeptide is called gonadotropin-releasing hormone (GRH). GRH is used to induce ovulation in infertile individuals. To achieve this effect, GRH must be administered as an intravenous infusion, pulsed (a small dose of GRH is injected every hour for several days),

because only then does the secretion of FSH and LH increase. On the other hand, synthetic GRH analogues (leuprolide, goserelin, triptorelin, etc.) act continuously on the pituitary gland and lead to the opposite effect - a decrease in the secretion of FSH and LH. Therefore, GRH analogues are used to treat sex hormone-dependent cancers (prostate cancer, breast cancer, etc.), endometriosis, hirsutism, and other diseases where it is desirable to reduce the release of FSH and LH. GRH analogues are administered parenterally, in the form of subcutaneous injections, because they are also peptides in chemical composition. After the administration of GRH analogues, patients experience hot flashes, erectile dysfunction, and loss of libido. A decrease in the secretion of FSH and LH can also be achieved with GRH receptor blockers: **degarelix, ganirelix, cetrorelix**.

FSH can be obtained in larger quantities from the urine of postmenopausal women (the preparation is called human menopausal gonadotropin HMG), while LH is not used as such, but instead human chorionic gonadotropin (a hormone of the corpus luteum and placenta found in large quantities in the urine of pregnant women hHG), which has very similar effects, is used. Both preparations are used sequentially to induce ovulation in patients suffering from infertility and to stimulate spermatogenesis in men. Human chorionic gonadotropin can sometimes cause the testicle to descend that has remained in the inguinal canal (undescended testis). Recently, human follicle-stimulating hormone (rFSH) has been synthesized by recombinant technology, which is the same or slightly more effective than human menopausal gonadotropin in terms of efficacy, and can therefore be used instead. Recombinant human luteinizing hormone (r-hLH) has also recently been successfully used instead of human chorionic gonadotropin. The use of gonadotropins has two possible complications: ovarian hyperstimulation syndrome and an increased incidence of multiple pregnancies.

Somatostatin is a 14-amino acid hypothalamic polypeptide that reduces the secretion of pituitary growth hormone (STH), primarily in acromegaly. In addition, somatostatin inhibits the secretion of many digestive tract hormones, so it is used in the treatment of gastrointestinal bleeding. Instead of somatostatin, its 8-amino acid analogue - octreotide - is more often used, which is more effective and has a longer duration of action. **Octreotide** is successfully used in the treatment of carcinoid syndrome, gastrinoma, glucagonoma and watery diarrhea syndrome, hypokalemia and achlorhydria. A side effect of this drug is the occurrence of biliary calculi due to inhibition of gallbladder motility. In addition to octreotide, there is another octapeptide analogue of somatostatin - lanreotide. **Lanreotide** has greater activity on subtypes 2 and 5 of the somatostatin receptor (there are 5 subtypes in total), which are the most important for controlling the secretion of somatotropin in the pituitary gland. It is used to treat acromegaly, neuroendocrine tumors and thyroid-stimulating adenomas.

Somatotropin is used to achieve normal height in people with dwarfism due to insufficiency of the anterior pituitary gland. In the past, STH was obtained by extraction from the pituitary glands of deceased people; however, since several cases of Creutzfeldt-Jakob disease (spongy degeneration of the central nervous system) due to the transmission of a type of protein (the so-called prion protein) have been identified, this hormone is no longer obtained in this way. Today, a recombinant analogue of the STH hormone, **somatropin**, is used. Growth hormone (somatotropin hormone) is also used successfully to treat cachexia in people with chronic diseases or acquired immunodeficiency syndrome.

Pegvisomant is a receptor blocker for somatotropin hormone, which is a protein by chemical nature. It is administered as a subcutaneous injection for the treatment of acromegaly that no longer responds to somatostatin or lanreotide.

The hypothalamus also produces **somatotropin-releasing hormone** (40 amino acids), which increases the secretion of STH from the pituitary gland. Its use in the treatment of dwarfism is still in the experimental phase. Its other name is **somatorelin**, and for now it is used only in diagnostics.

The secretion of thyroid-stimulating hormone by the pituitary gland is increased by a hypothalamic tripeptide called **thyrotropin-releasing hormone** (TRH). It is used only in the diagnosis of thyroid disease. **Thyrotropin** (TSH) is used in the treatment of thyroid cancer. When administered simultaneously with radioactive iodine (131J), TSH increases its entry into tumor cells and thus enhances the tumoricidal effect.

Prolactin secretion in the anterior pituitary is reduced by dopamine from the hypothalamus. Increased prolactin secretion (e.g. in pituitary adenoma) results in gynecomastia and impotence in men, and galactorrhea and amenorrhea in women. It can be suppressed by a dopamine analogue, one of the alkaloids of Ergot (Secale cornutum) - **bromocriptine**. In addition, bromocriptine is used to interrupt normal breastfeeding when necessary (for example, in breast abscesses) and to treat acromegaly (because it reduces the release of STH from pituitary tumors). The dose of bromocriptine for the cessation of lactation is 2.5 mg twice daily for two weeks. As a dopamine analog, bromocriptine is also a useful drug for the treatment of parkinsonism (see the chapter on parkinsonism). Side effects of bromocriptine include: dystonia (involuntary movements), confusional state with hallucinations, hypersexuality, and hypotension. In addition to bromocriptine, another dopamine receptor agonist, **cabergoline**, can be used to suppress hyperprolactinemia. The efficacy of cabergoline is similar to that of bromocriptine, but its effect is significantly longer, so it is usually administered in only one dose for the cessation of lactation.

The anterior pituitary gland also secretes adrenocorticotropic hormone (ACTH). ACTH controls the secretion of steroid hormones in the adrenal cortex. It is used exclusively in the diagnosis of adrenal diseases. The secretion of ACTH is also under

control: a hypothalamic peptide of 41 amino acids increases it (corticotropin-releasing hormone). Like ACTH, corticotropin-releasing hormone is used only for diagnostic purposes.

Hormones of the posterior pituitary gland

Neurons from the paraventricular and supraoptic nuclei of the hypothalamus send their axons to the posterior pituitary gland. The endings of these axons secrete two hormones: **oxytocin and vasopressin (antidiuretic hormone).** Both hormones are octapeptides.

Oxytocin causes contraction of the gravid uterus: its increased release leads to labor. It also contracts the myoepithelial cells around the acini of the mammary gland and leads to the secretion of milk during lactation. It is used to induce (start) labor in prolonged pregnancy and to stimulate uterine contractions during labor that is taking too long. It is then given i.v. infusion (5 IU of oxytocin is administered in 500 ml of 5% glucose, so that the infusion rate is initially 8 drops/min; the rate is then gradually increased to a maximum of 40 drops/min). Oxytocin can be administered as a nasal spray to nursing mothers with milk retention to improve breast emptying.

Recently, there has been increasing evidence that oxytocin stimulates protective behavior of the mother towards the child, and that it increases empathy and trust towards other people. Clinical studies are underway to show whether oxytocin will be useful in the treatment of autism.

Vasopressin (antidiuretic hormone) in physiological concentrations increases water reabsorption from the collecting ducts of the kidneys (by causing the incorporation of water channels into the luminal membrane of the cells of the collecting ducts). At concentrations about 100 times higher, it constricts the arteries and arterioles of the abdominal organs and the coronary arteries. Vasopressin is used in practice to treat diabetes insipidus and to reduce bleeding from ruptured esophageal varices (because it reduces blood flow through the abdominal organs). Since vasopressin is rapidly degraded in the body (t1/2 is about 10 minutes), the analogue desmopressin (1-desamino-8-D-arginine vasopressin) is used to treat diabetes insipidus, which is degraded more slowly (t1/2 is about 75 minutes) and can therefore be administered sublingually only twice a day.

Recently, it has been shown that the administration of vasopressin with adrenaline in patients with cardiac arrest reduces brain damage after resuscitation. This opens up the possibility that vasopressin could become a routine therapy for cardiac arrest.

Vasopressin receptor blockers, **conivaptan and tolvaptan**, which are used to treat hyponatremia in heart failure and the syndrome of inappropriate antidiuretic hormone (vasopressin) secretion, have also been included in the therapy.

ATOSIBAN

Atosiban is an oxytocin receptor blocker with a tocolytic effect, i.e. it relaxes the uterus, which contracts earlier or more than is physiological during pregnancy. Its efficacy in suppressing premature contractions and preventing premature birth is the same as that of β2-agonists or calcium channel blockers (nifedipine in particular), but it has one advantage: it exhibits fewer cardiovascular and neurological side effects than β2-agonists (tachycardia, hypotension, tremor) and calcium channel blockers (flushing, palpitations, hypotension).

The indication for the use of atosiban is the prevention of uncomplicated premature birth between the 24th and 33rd week of gestation. It is especially indicated in pregnant women who have concomitant heart disease.

Atosiban is administered by intravenous infusion for a maximum of 48 hours. First, 6.75 mg of atosiban is injected within one minute, then 18 mg/hour of the drug is administered for 3 hours, and the infusion rate is 6 mg/hour for the next 45 hours. In addition to atosiban, indomethacin (only if the gestation is shorter than 32 weeks), intravenous beta 2 agonists (terbutaline, ritodrine, hexoprenaline, fenoterol) or oral calcium channel blockers (primarily nifedipine) can be used to prevent preterm labor. In all cases, the use of therapy is limited to two days. Beta 2 agonists have the most side effects when used in this indication (prevention of preterm labor).

MEDICATIONS AGAINST DIABETES

Diabetes mellitus is a disease that results from a lack of insulin (a hormone produced by the pancreatic β-cells) and/or reduced sensitivity of peripheral tissues to insulin. It occurs in two forms: insulin-dependent diabetes (IDD or type 1) and non-

insulin-dependent diabetes (NID or type 2). IDD usually begins in childhood or early adolescence due to autoimmune damage to the pancreatic β-cells, while IND in later life due to exhaustion of the β-cells by continuous hyperstimulation (due to overeating). In IDD, insulin is practically absent in the blood, while glucagon levels are elevated. In IND, the level of insulin in the blood is usually sufficient to prevent the development of ketoacidosis, and reduced sensitivity of peripheral tissues to insulin and reduced response of pancreatic beta cells to glucose from the blood dominate. In principle, IDD is treated with insulin, and IND with oral hypoglycemic agents and/or insulin. Insulin is a peptide hormone (51 amino acids) composed of two chains linked by disulfide bonds.

It is formed by hydrolysis of proinsulin, a long protein chain, in the Golgi cisternae. From proinsulin, insulin and C-peptide are formed, which has no function. Insulin is then deposited in the granules of beta cells, where it forms crystals composed of six of its molecules and two zinc atoms. The activity of insulin is traditionally expressed in international units, but with the advancement of its production technology, highly purified preparations have been obtained, which are measured in weight units. Precise measurements have shown that 1 mg of insulin has an activity of about 28 IU. The entire human pancreas contains about 200 IU of insulin at any given time.

Insulin is degraded in the liver and kidneys by hydrolysis of disulfide bonds. The half-life of insulin is 4-5 minutes.

Insulin promotes the entry of glucose and amino acids into cells (by causing the appearance of transporters on the outer membrane), inhibits gluconeogenesis, and promotes glycolysis. It increases the synthesis of proteins and fats in peripheral tissues. It induces lipoprotein lipase and inhibits intracellular lipase. In the liver, it promotes the synthesis of glycogen and fatty acids from glucose.

Insulin preparations are administered only parenterally. Regardless of their origin (animal or human), insulin preparations are divided into ultrashort, short, medium, and long-acting.

Ultra-short-acting insulin is a preparation called insulin **lispro**, and it is obtained by recombinant technology (the insulin gene is inserted into microorganisms that then synthesize insulin). It differs from natural insulin in that two amino acids have swapped places: proline at position B28 and lysine at position B29. It is administered subcutaneously, reaches its maximum concentration in the blood after 1 hour, and acts for 3-4 hours. Two other insulin analogues have ultra-short action: **insulin aspart** and **insulin glulisine**. Ultra-short-acting insulins are suitable for use before meals, because the patient can start eating almost immediately.

Regular, **natural insulin (popularly called "crystalline")** is short-acting (its action begins in 30 minutes, reaches a maximum in 2-3 hours, and lasts 6-8 hours) and is the only one that can be administered both subcutaneously and intravenously. It is particularly suitable for intravenous administration in emergency situations: in ketoacidosis, after surgery, or during severe infections.

By adding zinc or protamine to insulin, preparations are obtained that gradually release insulin after s.c. administration and thus have a medium-long or long-lasting effect. In recent years, the use of protamine has been avoided. Medium-long-acting insulin is **lente** (a mixture of 30% semilente insulin and 70% ultralente insulin; semilente insulin - an amorphous form of insulin (does not crystallize) that acts briefly, but is no longer used on its own) and **isophane insulin** (a mixture of insulin and protamine). Their action begins in about 2 hours and lasts up to 24 hours.

Long-acting insulin ultralente and protamine-zinc-insulin, which have even larger amounts of zinc or protamine added, are long-acting. Their action begins in 4 hours and lasts up to 36 hours. All preparations except crystalline can only be administered subcutaneously. A new long-acting preparation of insulin is **glargine**. It contains two more arginine molecules than natural insulin at the COOH-end of the B chain, and instead of asparagine at position A21, it has glycine. Glargine has the advantage over other preparations in that it provides a steady insulin level for more than 24 hours (without peaks). Another insulin analogue, insulin **detemir**, which has a saturated fatty acid added to the amino group of lysine 29, behaves similarly. Another long-acting insulin analogue is **insulin degludec**, which causes hypoglycemia less often than insulin ultralente or protamine zinc insulin. An extremely long-acting insulin analogue (maximum concentration is achieved after 16 hours, and the half-life is 7 days) is called **icodex**, and is administered **once a week**. Studies have shown that it is equally effective as insulins administered daily, and that it is not inferior in terms of safety. Usually, insulin preparations of animal origin contain a mixture of two types of insulin (e.g., bovine insulin and porcine insulin); sometimes, however, the preparation is prepared from insulin of only one type (e.g., only from bovine or porcine). Such insulins are called "monocomponent" and are used in the event of the appearance of antibodies to insulin of one animal species. Today, insulins of human origin are almost always used instead of insulin of animal origin. They are less immunogenic, so resistance to them develops more slowly.

The classic insulin administration regimen involves the administration of a fixed daily dose of medium- or long-acting insulin that provides a basal level of the hormone, and the additional administration of short- or ultra-short-acting insulin before each meal. For easier administration, so-called mixed preparations are increasingly being made, which contain medium-acting insulin (usually isophane insulin) and insulin lispro, and which can be administered once or twice a day.

In patients who cannot achieve glycemic control with the usual dosing regimen, intensive treatment with continuous infusion of natural insulin should be applied. The infusion is administered subcutaneously, in the abdomen, with the help of programmed peristaltic pumps.

Early administration of insulin slows down the development of diabetes complications, as well as intensive therapy with precise glycemic control. Insulin-dependent diabetes is always treated with insulin. Patients with insulin-independent diabetes are transferred to insulin therapy in the following cases: (1) when they need to undergo surgical intervention; (2) when they get a severe infection and (3) during pregnancy.

Side effects of insulin are:
a) hypoglycemia (plasma glucose below 2.5 mMol/l) - occurs if insulin is overdosed or not accompanied by an appropriate diet. The patient experiences signs of sympathetic activation (tremor, sweating, hunger, fear, tachycardia) and, if nothing is done, confusion, convulsions and coma occur. Hypoglycemia is treated i.v. by administering 50 ml of 50% glucose (after the injection, it is mandatory to inject physiological saline to wash the vein, otherwise thrombophlebitis occurs), glucagon (1 mg s.c.) or, if the patient is conscious and in the early phase of hypoglycemia, by oral administration of glucose
b) atrophy of fatty tissue at the site of s.c. injections (avoided by frequently changing the site of administration)
c) insulin resistance due to the formation of antibodies (antibodies are formed even to human insulins!)
d) allergy to insulin of the first or third type.

Oral hypoglycemic agents are used only in the treatment of IND. There are several groups of oral hypoglycemic agents according to their chemical structure and mechanism of action: sulfonylurea derivatives, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase blockers, incretin analogues, dipeptidyl peptidase type 4 blockers, SGLT-2 inhibitors, aldose reductase inhibitors and glitazars.

Sulfonylurea derivatives (first generation: tolbutamide, chlorpropamide; second generation: glyburide, glipizide, glimepiride) close K+ channels in the beta-cell membrane, causing membrane depolarization, entry of Ca++ ions and release of insulin. Calcium causes contraction of myosin fibrils which leads to exocytosis of insulin granules and release of insulin. In addition to increasing insulin secretion, these drugs reduce glucagon secretion, which contributes to the control of hyperglycemia. There is no significant difference in efficacy among the drugs in this group, only the second-generation drugs have slightly fewer side effects. Problems in their use are the possibility of hypoglycemia, alcohol intolerance (due to disulfiram-like effects /chlorpropamide/), the occurrence of neutropenia, dilutional hyponatremia and increased appetite. Sulfonylurea derivatives are contraindicated in pregnancy (because they are teratogenic) and in liver disease. Chlorpropamide has a mild antidiuretic effect, so it can be used to treat milder forms of diabetes insipidus.

Meglitinides (repaglinide) began to be used only in 1998. They act by a very similar mechanism to sulfonylurea derivatives, i.e. they increase the release of insulin from beta cells. They act quickly and briefly (up to 2-3 hours), so they are used to control postprandial spikes in blood glucose (taken immediately before meals).

Biguanides (metformin) promote the entry of glucose into the cells of peripheral tissues and reduce glucose production in the liver, so they are effective even in patients who no longer have functional beta-cells in the pancreas. They also reduce glucagon levels. They almost never cause hypoglycemia, so they are called "euglycemic" drugs. Their disadvantages are their tendency to cause lactic acidosis, a metallic taste, and loss of appetite. Metformin is well absorbed and excreted unchanged in the urine. It has a short half-life of 2-3 hours.

Metformin is most commonly used in patients who are obese and in whom hyperglycemia is the result of tissue insensitivity to insulin. It is also used in combination with sulfonylureas, if they alone cannot control glycemia. Metformin should be used with caution in patients with renal insufficiency, as metformin accumulation and lactic acidosis may occur.

In patients with non-IDD who do not respond to diet or diet and the previously mentioned hypoglycemics, the sugar **acarbose** can be used. Acarbose is not absorbed and inhibits the enzymes ***sucrase and maltase*** (another name for these enzymes is alpha-glucosidase) located on the luminal membrane of the small intestine epithelium. Inhibition of these enzymes makes it difficult to digest disaccharides (sucrose, maltose) and thus slows down and reduces glucose absorption. In clinical studies to date, acarbose has been shown to reduce the concentration of glycosylated hemoglobin in patients, but it is not yet clear whether this drug can slow the onset of complications in diabetes or delay the use of insulin. In most patients, acarbose causes bloating, abdominal pain, or diarrhea, but these symptoms often resolve over time. Higher doses of this drug can cause chemical hepatitis. The good thing about acarbose is that it does not cause hypoglycemia.

Thiazolidinediones are newer drugs (**rosiglitazone and pioglitazone**) that act on peripheral tissue cells by mimicking the action of insulin. They actually bind to the "peroxisome proliferator-activated receptor gamma" (PPAR gamma), activate it, and

then the drug-PPAR gamma complex enables the expression of genes encoding enzymes distal to the insulin receptor. In addition, these drugs lead to fat redistribution: visceral fat tissue decreases and peripheral fat tissue increases.

Rosiglitazone and pioglitazone rarely cause hypoglycemia. They reduce triglyceride levels and increase HDL and LDL lipoprotein levels. The most significant side effect is **heart failure**, which is why rosiglitazone has been withdrawn from use in most countries. Pioglitazone is still in use, but prescribers are advised to closely monitor patients for early signs of heart failure. Other side effects include mild anemia, edema, and induction of cytochrome P450 in the liver, which may reduce the effects of other drugs (e.g., oral contraceptives). Clinically, pioglitazone is used to treat non-insulin-dependent diabetes, alone or in combination with biguanides.

Incretin-like drugs

Incretins are gastrointestinal hormones that are released into the blood after food reaches the stomach and duodenum. Their function is to facilitate the absorption and utilization of nutrients, especially glucose. The two most important incretins are **glucagon-like peptide 1 (GLP1**) and **glucose-dependent insulinotropic polypeptide 1 (GDIP-1)**. It has been observed that in type 2 diabetes, GLP1 secretion decreases, and that supplementation of this hormone improves glycemic control in patients with this disease. Recently, drugs that replace or enhance the action of endogenous incretins have been introduced into clinical practice. **Exenatide, liraglutide, and semaglutide** are GLP1 receptor agonists. Exenatide was isolated from the saliva of the venomous Gila Monster lizard. All three drugs are administered by subcutaneous injection, with an oral form of semaglutide recently developed. Like GLP1, exenatide, liraglutide, and semaglutide inhibit glucagon secretion, delay gastric emptying, increase insulin secretion, and reduce appetite through central action. All of these effects ultimately lead to normalization of blood glucose levels. They are used as add-on therapy in patients who are unable to achieve glycemic control with two oral antidiabetic agents (one sulfonylurea plus one biguanide). Semaglutide is also used in extremely obese individuals (BMI > 30) to reduce appetite and normalize body weight. The main adverse effects are hypoglycemia, gastrointestinal symptoms, and antibody formation.

Recently, a drug that simultaneously activates both glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide 1 (GDIP-1) has been introduced into clinical use. This dual agonist is a synthetic peptide with 39 amino acids and is called **tirzepatide**. It has the same effects as natural incretins, so it is used to treat diabetes that responds poorly to insulin. It also has other positive effects: it lowers blood pressure, reduces cholesterol and triglyceride levels in the blood.

Saxagliptin, vildagliptin and sitagliptin inhibit dipeptidyl peptidase 4, which results in a decrease in the breakdown of incretins (glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide 1), which accumulate and lead to increased insulin secretion, decreased glucagon secretion and slowed gastric emptying. They are used in type 2 diabetes alone or in combination with other oral antidiabetic drugs, in situations where other antidiabetic drugs do not work sufficiently. They are administered orally and are well tolerated..

SGLT-2 inhibitors (Sodium–Glucose Cotransporter 2 inhibitors) are drugs that block the transport of glucose from the lumen of the renal tubules back into the bloodstream, so that glucose is lost in the urine. Due to the decrease in blood glucose, the amount of glucose transporter type 4 increases, which brings glucose into striated muscle cells, and reduces gluconeogenesis in the liver. This group includes **dapagliflozin and canagliflozin**. These drugs can be combined with other antidiabetic drugs. They increase the frequency of urogenital tract infections and lead to hypotension; they rarely cause hypoglycemia.

The newest group of antidiabetic drugs (still in the testing phase) consists of **glitazars: muraglitazar and tesaglitazar**. Glitazars activate both PPAR alpha and PPAR gamma, leading to both triglyceride and glycemic reductions, two disorders that often coexist in patients with type 2 diabetes. Muraglitazar and tesaglitazar have not yet been approved for widespread use because clinical studies have shown that they increase the risk of heart failure and transient ischemic attacks.

Amylin

Amylin is a hormone secreted together with insulin from the beta cells of the islets of Langerhans. It reduces glucagon release, slows gastric emptying, and reduces hunger through its central action. **Pramlintide**, a synthetic analogue of amylin, is administered subcutaneously, immediately before meals, in patients with type 1 and type 2 diabetes. It helps regulate blood sugar in patients who do not respond to conventional therapy.

The main side effects of pramlintide are hypoglycemia and gastrointestinal complaints.

Glucagon

Glucagon is a peptide hormone secreted by the α-cells of the pancreas. It causes glycogenolysis and the release of glucose from the liver; it also increases the force of cardiac contraction.

Glucagon is used to treat hypoglycemic coma and acute heart failure. It is administered parenterally (i.v., i.m. or s.c.) at a dose of 1 mg.

The use of glucagon is contraindicated in patients with pheochromocytoma, as it leads to the sudden release of large amounts of catecholamines from the tumor.

Drugs that reduce the incidence of microangiopathy as a complication of diabetes (and subsequent retinopathy, nephropathy, neuropathy, diabetic foot)

Today, it is believed that microangiopathy as a complication of diabetes occurs due to the formation of free oxygen radicals and the accumulation of sorbitol in endothelial cells. Therefore, antioxidants (primarily **alpha-lipoic acid)** and aldose reductase inhibitors, an enzyme that reduces glucose to sorbitol, are used to prevent microangiopathy in diabetics. Of the aldose reductase inhibitors, **epalrestat** has entered clinical use. While alpha-lipoic acid only reduces the symptoms of neuropathy to some extent, epalrestat slows the progression of microangiopathy if administered in the early stages of its development. Epalrestat is administered orally and is well tolerated, as no serious adverse effects have been reported in clinical studies to date.

THYROID HORMONES AND ANTITHYROID DRUGS

The synthesis of thyroid hormones (triiodothyronine - T3 and tetraiodothyronine - T4) begins with the transport of iodine ions (I-) into the cells of the thyroid gland. Iodine is then oxidized to elemental iodine (I) by thyroperoxidase and binds to molecules of the amino acid tyrosine. This process is called iodine organification. The iodinated tyrosine is now incorporated into thyroglobulin, a protein that forms the main component of the colloid of the thyroid follicle. Other iodinated tyrosine molecules are added to the already incorporated tyrosine molecules, forming T3 or T4. When T3 and T4 need to be released into the circulation, the follicle cells phagocytose the colloid and transport it to their lysosomes. In the lysosomes, thyroglobulin is broken down and T3 and T4 are released into the bloodstream (the ratio of T4 to T3 is 5:1). In the blood, most of these hormones are bound to globulins (99.5%), and a smaller part is free and active. T4 is converted in the tissues to T3, which is the active form of the hormone. T4 and T3 enter the cells they affect, bind to their receptors in the nucleus, and induce the expression of genes for numerous enzymes and functional proteins.

Some drugs (ipodate, corticosteroids, beta-blockers), as well as severe illness or starvation, inhibit 5'-deiodinase, which normally converts T4 to T3. Therefore, most of the T4 is converted to the inactive form of T3, the so-called reverse triiodothyronine (rT3), leading to a decrease in the effect on target tissues.

The secretion of thyroid hormones is under the control of the pituitary thyroid-stimulating hormone (TSH). This hormone stimulates the enzyme adenylate cyclase in thyroid cells, thereby increasing the synthesis and secretion of T4 and T3. The secretion of TSH itself is controlled by the hypothalamic hormone, TRH (thyrotropin-releasing hormone), whose release depends on the levels of T4 and T3 in the blood (negative feedback).

Thyroid hormones enable the synthesis of many enzymes necessary for normal cell function. Their presence is necessary for the normal action of STH hormone (and thus growth); oxidative metabolism processes are accelerated, producing larger amounts of energy phosphates and releasing a larger amount of heat. In addition, thyroid hormones increase the number of beta-receptors and thus sensitize peripheral tissues to the effects of catecholamines. Thyroid hormones are used to treat hypothyroidism and goiter. T4 is most commonly administered orally. Therapy should be started with low doses and then gradually increased, so that vital organs (primarily the heart) gradually adapt to new metabolic needs. The usual dose is 100 - 150 mcg/24 hours, orally. T3 is administered only in patients in myxedema (hypothyroidism) coma, as an intravenous injection (10 mcg/12 hours slowly i.v.). Many authors believe that it is safer to administer T4 intravenously. In people with heart disease, the administration of thyroxine can lead to tachycardia, arrhythmias and, (if the coronary arteries are narrowed), to angina pectoris or myocardial infarction.

It is especially important to detect and treat hypothyroidism during pregnancy, because insufficient secretion of thyroid hormones can lead to permanent damage to the child's brain and later reduced intelligence. During pregnancy, the need for thyroid hormones increases, so the supplemental doses are higher than those normally given.

Hyperthyroidism can be treated in several ways. One of them is the use of drugs that inhibit the incorporation of iodine into tyrosine, i.e., the synthesis of thyroid hormones. These are thionamides: methimazole and propylthiouracil. These drugs take 3-4

weeks to work, until the hormone stores in the thyroid gland are depleted. Therapy with these drugs lasts about a year, and then is stopped. In half of the patients, the disease recurs after about a year, so it is necessary to apply the mentioned drugs again. The disadvantage is their tendency to cause neutropenia and other blood disorders, so blood counts should be monitored during therapy (any tonsillopharyngitis in patients taking these drugs can be a sign of neutropenia!). They also cause vasculitis and jaundice in a small number of patients. Propylthiouracil is not teratogenic, while methimazole causes fetal head defects after administration during pregnancy. Therefore, propylthiouracil is always used in the case of hyperthyroidism in pregnant women. Also, breastfeeding is possible in the presence of propylthiouracil.

Adverse reactions to thionamides occur in about 10% of patients. The most common adverse reaction is a maculopapular rash, sometimes accompanied by fever. Rarely, liver damage, swelling of the lymph nodes, and symptoms similar to those occurring in systemic connective tissue diseases may occur. Agranulocytosis occurs in about 0.5% of patients.

Hyperthyroidism can also be treated with the use of radioactive iodine (I131), which is now known not to increase the risk of malignant diseases of the neck. Radioactive iodine is rapidly and completely absorbed, and then concentrated in the thyroid gland. Only one dose is administered, which often leads to hypothyroidism, requiring lifelong thyroid hormone replacement therapy. Radioactive iodine should not be administered to pregnant women and nursing mothers, as it crosses the placenta and is excreted in milk. Iodides in larger amounts (doses) also suppress thyroid function. They reduce the release of thyroid hormones, and improvement can be observed as early as 1 day after administration. The maximum effect is seen 3-7 days after administration. Iodides also inhibit organification and reduce blood flow to the gland, which becomes smaller and firmer. Therefore, iodides are most commonly used in the preoperative preparation of patients for whom thyroidectomy is indicated. Side effects of iodides include skin acne, swelling of the salivary glands, and a metallic taste in the mouth.

Iodides cannot be used alone to treat hyperthyroidism for long periods of time. After 2-8 weeks, the effect wears off, and then a very severe form of hyperthyroidism develops because the thyroid gland is extremely rich in iodine.

Treatment of thyrotoxic storm

Thyrotoxic storm is an acute exacerbation of hyperthyroidism accompanied by hyperthermia, hyperkinetic blood flow and often heart failure. In this case, the effects of thyroid hormones on the heart should be quickly suppressed. This is achieved by administering beta-blockers (e.g. propranolol, 1 mg i.v., repeated several times if necessary) that eliminate the influence of catecholamines (T3 and T4 otherwise increase the sensitivity of the heart to catecholamines), propylthiouracil (500 mg loading dose, then 250 mg every 6 hours orally) and iodinated contrast agents that block the peripheral conversion of T4 to the active form T3. After a few days, propylthiouracil should be replaced by methimazole due to less hepatotoxicity and more effective control of serum T3 levels.

Iodides are also used (which noticeably reduce the release of thyroid hormones after just one day /0.5 ml/8 hours of Lugol's solution, orally/) and high doses of corticosteroids (e.g., dexamethasone 4 mg/6 hours orally). Iodides should be used only after the use of propylthiouracil, so as not to cause a temporary worsening of hyperthyroidism due to the high rate of iodide reaching the thyroid gland. Oral administration of cholestyramine resin is also useful, as it binds thyroid hormones and prevents their reabsorption. In addition, the patient must have high-quality care, fluid and electrolyte replacement, and nutrition.

Table 17. Doses of antithyroid drugs

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Methimazole	Oral	10 mg	8 h
Propylthiouracil	Oral	200 mg	8 h
Ipodate (iodinated contrast agent)	Oral	0.5 g	24 h*

* only for three days.

ADRENAL CORTEX HORMONES

The adrenal cortex has three layers, from the outside in: the zona glomerulosa (where aldosterone is synthesized), the zona fasciculata (where cortisol is synthesized), and the zona reticularis (where androgens are synthesized). Aldosterone is a mineralocorticoid that increases the reabsorption of sodium ions and, at the same time, the secretion of potassium ions in the distal tubules of the kidneys. Aldosterone secretion is largely controlled by angiotensin 2; higher levels of this peptide in the blood mean

greater aldosterone secretion. Namely, increased sodium loss in the renal tubules leads to the release of renin, which then leads to the formation of angiotensin 1; angiotensin 1 is converted to angiotensin 2 by peptidyl dipeptidase in the lungs, which in turn increases aldosterone secretion. Only a small part of aldosterone secretion is under the control of the pituitary ACTH hormone. Insufficient aldosterone secretion (Addison's disease) is treated with a synthetic steroid with mineralocorticoid activity: fludrocortisone (dose: 0.1 mg/24 hours, orally).

Cortisol and other glucocorticoids, as lipophilic substances, easily diffuse through the membrane of the cells they act on. In their cytoplasm, there is a receptor for cortisol that is in a resting state bound to two molecules of the so-called heat-shock protein (heat-shock protein), which is designated Hsp90. Upon the arrival of cortisol, Hsp90 dissociates from the receptor, and cortisol binds to it. The cortisol-receptor complex then goes to the nucleus and binds to the promoters of a number of genes. By binding to the promoters, these complexes actually activate the transcription of these genes, i.e. their expression. Since it acts through gene expression and de novo protein synthesis, the clinical effects of cortisol are manifested only after a latent period of about 30 minutes; for the full manifestation of the effects it takes up to 24 hours.

Cortisol inhibits glycolysis, increases glycogen synthesis in the fasting state, intensifies gluconeogenesis in the liver, and increases blood glucose levels. It also promotes lipolysis and proteolysis in muscle and adipose tissue, increasing the delivery of free fatty acids and amino acids to the liver. The purpose of cortisol's action in the period between two meals is to ensure sufficient amounts of glucose in the blood necessary for brain nutrition. In addition to metabolic effects, cortisol also exerts the following effects:

a) **anti-inflammatory** (blocks phospholipase A2, which enables the synthesis of prostaglandins and leukotrienes; reduces the expression (synthesis) of cyclooxygenase II, which is necessary for the synthesis of prostaglandins; inhibits the release of inflammatory mediators from mast cells and eosinophils; inhibits the activity of adhesive molecules on endothelial cells by which leukocytes exit capillaries)

b) **antiedematous** (reduces capillary permeability by reducing the release of histamine from basophils and mast cells)

c) **immunosuppressive** (inhibits the activity of T-helper lymphocytes, prevents the synthesis and release of interleukins 1 to 6, in high doses reduces the formation of antibodies)

d) **antineoplastic** (reduces the number of pathological lymphocytes)

e) **reduction in the number of lymphocytes, eosinophils, basophils and monocytes, and an increase in the number of neutrophils, platelets and erythrocytes in the blood**

f) **catabolic effect** on connective tissue, skin, bone tissue, muscles and adipose tissue

g) increased cortisol concentration in the blood initially leads to **insomnia and euphoria**, and later to **depression**; Extremely high doses of glucocorticoids can lead to increased intracranial pressure.

h) Cortisol is necessary for normal **maturation of surfactant** in the fetal lungs during the last weeks of gestation.

Although cortisol is also used as a drug (**hydrocortisone**), a large number of preparations with glucocorticoid activity have been synthesized. The most commonly used are: ***prednisone*** (which is converted in the liver to its active form, ***prednisolone***) orally, ***prednisolone*** (4 times more potent than cortisol) orally, ***methylprednisolone*** (5 times more potent than cortisol) orally and parenterally, ***dexamethasone*** (40 times more potent than cortisol, has no mineralocorticoid activity) orally and parenterally, ***beclomethasone, fluticasone, mometasone, ciclesonide and budesonide*** (only in aerosol form, for the treatment of asthma). ***Triamcinolone acetonide*** is a moderately potent corticosteroid that is used as an intravitreal injection or implant for the treatment of macular edema in diabetics. For the treatment of skin diseases, ***clobetasol*** (ultra-potent corticosteroid), ***fluocinonide*** and ***betamethasone*** (high-potency), and ***triamcinolone acetonide*** (moderate-potency) are used topically in the form of ointments or creams.

Corticosteroids are used to treat adrenocortical insufficiency, bronchial asthma (intravenously or orally to stop severe asthma attacks, and by inhalation to prevent attacks), autoimmune diseases, allergic reactions, brain edema (dexamethasone), soft tissue edema after dental surgery (dexamethasone), excessive inflammatory reactions in viral pneumonia (dexamethasone), lymphatic leukemias, and to prevent transplant rejection. Cortisol is also used in the treatment of congenital adrenal hyperplasia; hyperplasia occurs due to deficient cortisol synthesis and subsequent increased ACTH secretion. Towards the end of pregnancy, corticosteroids can accelerate lung maturation (increase surfactant synthesis) and prevent the occurrence of respiratory distress syndrome in the child if premature birth occurs.

When used in large (pharmacological) doses, corticosteroids have many side effects. They increase **gastric acid secretion**, lead to **osteoporosis**, skin **atrophy**, **psychotic** manifestations, **hypertension**, cataracts, and adrenal atrophy (due to suppression of ACTH release). The risk of fungal, viral, and mycobacterial infections increases. Side effects occur after prolonged use of corticosteroids; use for up to 7 days is not associated with significant side effects. When corticosteroids are used for a longer period, discontinuation of therapy must be gradual, otherwise symptoms and signs of adrenal insufficiency may occur.

When administered in the first trimester of pregnancy, corticosteroids increase the risk of cleft palate. If systemic administration of corticosteroids during pregnancy is necessary due to the nature of the mother's disease, the drug of choice is prednisone, because the fetal liver cannot be converted to prednisolone, its active form, and the fetus is therefore less exposed to harmful effects than if other corticosteroids are administered.

Androstenedione and dihydroepiandrosterone, which are secreted in the zona reticularis, normally constitute a small part of the total androgens in men and women. In postmenopause, they become the main source from which estrogens are produced by aromatization in adipose tissue.

The synthesis of all adrenal hormones can be completely blocked by **aminoglutethimide**, a blocker of the enzyme that converts cholesterol to pregnenolone, the first step in steroid synthesis. This effect is used in the treatment of some hormone-dependent tumors of the prostate or breast. **Mitotane** is a drug that destroys adrenal cortex cells; it is used for the palliative treatment of inoperable adrenal cortex carcinomas. Many drugs have a side effect of blocking the synthesis of steroid hormones in the adrenal gland. Among them, drugs with the imidazole group stand out: the fungicide ketoconazole, the H2 receptor blocker cimetidine, and the proton pump blocker omeprazole.

Table 18. Corticosteroid dose according to indications

DRUG	INDICATION	ROUTE OF ADMINISTRATION	DOSE
Cortisol (hydrocortisone)	Адисонова болест	Oral	10 mg/12 h
Hydrocortisone-sodium succinate	Addison crisis (acute failure of suprarenal gland)	i.v.	50 mg/6 h
Prednisone	Asthma	Oral	30 mg/day
	Systemic erythematoid lupus	Oral	30 mg/day
Methylprednisolone - sodium succinate	Anaphylactic shock	i.v.	40 mg
Dexamethasone	Brain edema	i.m.	20 mg/day

ESTROGENS

Estrogens are steroid hormones secreted in the ovary (especially in the 1st phase of the menstrual cycle), and during pregnancy in the placenta. A significant part of estrogen is produced in adipose tissue, where the androgen androstenedione originating from the adrenal cortex is converted into estrone under the action of aromatase. Natural estrogens are estradiol, estrone, estriol and estetrol. A large number of preparations with estrogenic action have been synthesized, some of which are steroid structures (ethinyl estradiol, mestranol) and some are not (diethyl stilbestrol, chlorotrianisene).

Estrogens bind to their intracellular receptors with which together (in a complex) they regulate the synthesis of a large number of enzymes and structural proteins. The effects of estrogen are:

- trophic effect on the uterus, vagina, vulva and skin in general;
- stimulation of the growth of the mammary gland ducts;
- in the 1st phase of the menstrual cycle, estrogens lead to the growth of the endometrium;
- slowing down bone resorption;
- increase in HDL in the blood and decrease in LDL lipoproteins (anti-arteriosclerotic effect);
- increase in the level of coagulation factors in the blood.

Estrogens are used as ***replacement therapy in postmenopause*** because they prevent osteoporosis and relieve climacteric symptoms (hot flashes, irritability, instability of the autonomic nervous system). Their use for this indication should be limited to the age up to 60, because in older women they excessively increase the risk of thromboembolism and breast cancer. If a menopausal woman only has local symptoms due to atrophic changes in the vagina and trigone of the bladder, then it is sufficient to apply vaginal preparations with low estrogen concentrations. In women of reproductive age, estrogens can stop menorrhagia or metrorrhagia. Estrogens can also suppress the growth of prostate tumors and some breast tumors. Together with gestagens, they are used as oral contraceptives.

Side effects of estrogens include: increased incidence of thrombosis, hypertension, breast tenderness, confusion, increased risk of endometrial and breast cancer, nausea and vomiting. Natural estrogens are administered only parenterally, because after

oral administration and absorption in the intestines, they are metabolized during the first pass through the liver, so none of the drug would reach the systemic circulation. Synthetic estrogens or conjugated natural estrogens are broken down much more slowly, so their oral administration is possible.

Table 19. Doses of the most commonly used estrogens.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Chlorotrianisen	Oral	12 mg	24 h
Conjugated estrogens	орално	0.5 mg	24 h
Estradiol cypionate (depo form)	i.m.	1.5 mg	4 weeks

PROGESTOGENS

Progestogens are substances that act similarly to the natural ovarian hormone progesterone. The most similar to progesterone are steroids with a 21C atoms, which we call **pregnanes** (**medroxyprogesterone, megestrol**); another large group of progestogens consists of 19-nortestosterone derivatives, which we call **estranes** (**norethindrone, noretinodrel, ethynodiol**). The third group of synthetic progestogens consists of drugs called **gonanes**: **levonorgestrel, desogestrel, gestodene, norgestimate**. Progestogens also include a derivative of spironolactone, **drospirenone**. Progesterone and progestogens act by binding to their intracellular receptors and regulating gene expression.

Progesterone increases body temperature, has a depressant effect on the central nervous system, promotes the development of mammary alveoli and secretory maturation of the endometrium in the 2nd phase of the menstrual cycle. It also relaxes smooth muscle.

Progestogens are used to treat irregular menstrual bleeding, endometriosis, and dysmenorrhea. They are also an integral part of combined estrogen-gestagen preparations for hormone replacement in postmenopausal women and for contraception. Combined estrogen-gestagen contraceptive preparations are also used to treat: oligomenorrhea in polycystic ovary syndrome, menstrual migraine, suppression of ovarian cyst growth, and hyperandrogenism in polycystic ovary syndrome (gonads only).

Progesterone is used to prevent miscarriage in pregnant women who have early bleeding in pregnancy and who have already had several spontaneous miscarriages. However, its use in pregnancy is controversial, as it increases the incidence of hypospadias in male newborns! In non-pregnant women, progesterone can cause depression and edema. 19-nortestosterone derivatives have significant androgenic side effects: they can cause hirsutism (increased male-pattern hairiness), acne, skin pigmentation, and a decrease in plasma HDL lipoprotein levels. Gonanes have a less pronounced androgenic effect, and they do not act on estrogen receptors. Some of the new progestogens even block androgen receptors: dienogest, drospirenone, and trimegestone.

Table 20. Doses of the most commonly used progestogens.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL	INDICATION
Medroxyprogesterone acetate	Oral	5 mg	24 h	Irregular menstrual bleeding
	i.m. (depo)	500 mg	7 days	Certain types of breast cancer
Progesterone	i.m.	10 mg	24 h	Irregular menstrual bleeding
Norethisterone	Oral	5 mg	12h (from 5th day of menstrual cycle)	Endometriosis

PROGESTERONE ANTAGONISTS

A progesterone receptor blocker is **mifepristone**. It is used to induce abortion in early pregnancy (up to 7 weeks old): 400 mg of mifepristone is given daily for 4 days. It can also be used effectively for postcoital contraception: just one dose of 600 mg immediately after coitus can prevent fertilization of the egg and the formation of a zygote.

SELECTIVE PROGESTERONE RECEPTOR MODULATORS

Selective progesterone receptor modulators are drugs that act on the progesterone receptor in different ways in different tissues. ***Ulipristal acetate*** is administered orally, and prevents endometrial proliferation, prevents further growth of uterine fibroids, and reduces gonadotropin secretion in the pituitary gland. It is primarily used to relieve symptoms of uterine fibroids (prolonged bleeding) before surgery or occasionally in patients who are not candidates for surgery. The drug is well tolerated, with the only side effects being flushing of the face and neck with a feeling of warmth, and thickening of the endometrium that requires ultrasound monitoring. It is metabolized in the liver by cytochrome 3A4.

ESTROGEN RECEPTOR BLOCKERS

Fulvestrant is a competitive estrogen receptor blocker. It is used for the treatment of postmenopausal women with metastatic or locally advanced estrogen-dependent breast cancer, provided that the disease has not responded to other antiestrogen drugs. It is administered intramuscularly, in a single dose once a month. Side effects include thromboembolism and liver damage with increased serum bilirubin. Fulvestrant is metabolized in the liver to active metabolites, both via cytochrome 3A4 and via alternative pathways.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Selective estrogen receptor modulators are synthetic drugs that activate or block estrogen receptors in some tissues, but have no effect in others. They were synthesized with the idea of creating drugs that would have the desired effects of estrogen, but would not exhibit the side effects characteristic of estrogens.

The first estrogen receptor modulator was **tamoxifen**. It is used to treat estrogen-dependent breast tumors, i.e. those that have estrogen receptors in their cells, primarily in postmenopausal women. It is administered orally, at a dose of 10 mg/12 hours. Side effects of tamoxifen are vomiting and "hot flashes". In addition to tamoxifen, **toremifene** is also used to treat estrogen-dependent breast tumors. Toremifene also causes nausea and hot flashes, and in addition increases the tendency for thrombosis and prolongs the QT interval, which can lead to ventricular arrhythmias.

Raloxifene is a selective estrogen receptor modulator used to treat osteoporosis in perimenopausal women, as it reduces bone resorption. It is also used to reduce the risk of invasive breast cancer in postmenopausal women who are otherwise at high risk. Raloxifene can cause venous thrombosis and fatal stroke.

Ospemifene acts as an agonist of estrogen receptors in the vulva, vagina and bone, as an antagonist of receptors in the breast and as a partial agonist of receptors in the uterus. This profile of action allows its use in the treatment of vulvovaginal atrophy in menopausal women, which otherwise greatly reduces the quality of life. Ospemifene is administered orally and has few side effects, the most common of which are hot flashes.

Clomiphene blocks estrogen receptors in the pituitary gland, leading to increased release of gonadotropins. This mechanism of action is the reason clomiphene is used to stimulate ovulation in women undergoing infertility treatment. Side effects of clomiphene include ovarian enlargement, hot flashes, and nausea.

AROMATASE INHIBITORS

Aromatase is an enzyme found in adipose tissue, muscle, liver, and mammary glands; this enzyme converts the androgen androstenedione to estriol, which is the main source of estrogen in postmenopausal women. Aromatase inhibitors can be used as adjunctive therapy for breast cancer (both early and advanced disease) in postmenopausal women (provided that the cancer contains estrogen receptors). Previously, aminoglutethimide, a drug that also blocks the synthesis of steroid hormones in the adrenal cortex, was used for this purpose. Today, selective aromatase inhibitors are available that have few side effects and are effective. Some of these drugs are **letrozole, anastrozole, and exemestane**. A common side effect of these three drugs is osteoporosis accompanied by joint pain (arthralgia) due to reduced bone density (aromatase inhibitor-associated arthralgia syndrome); Letrozole and anastrozole, in addition to osteoporosis, also cause hypercholesterolemia.

ORAL CONTRACEPTIVES

Oral administration of estrogen, progestogen, or a combination of estrogen and progestogen can effectively prevent conception. Since the use of estrogen alone is associated with too high a risk of side effects, today only a combination of estrogen and progestogen or only progestogens are used. The combination of estrogen and progestogen inhibits the release of FSH and LH from the pituitary gland and thus prevents ovulation; the endometrium becomes inhospitable to the implantation of the zygote, and the cervical mucus remains thick throughout the cycle. The combination is taken from the 7th day after the start of menstruation to the 28th day. After stopping the intake, menstruation occurs, and the intake of the preparation is continued in the next cycle.

In addition to contraception, these drugs can be used (off-label) for irregular menstrual cycles, excessive menstrual bleeding, endometriosis pain, and prevention of migraine associated with menstruation.

A progestogen-only pill is taken continuously, without a break. The progestogen makes the endometrium inhospitable to the zygote and the cervical mucus thick and impenetrable to sperm. Although they inhibit the release of LH from the pituitary gland, progestogen-only pills prevent ovulation in only 40% of cycles. Despite continuous use of progestogen, irregular menstrual bleeding occasionally occurs.

Combined pills prevent conception in 99% of cases, and progestogen-only pills in 97%.

Side effects of estrogen from contraceptives include: increased blood coagulation factors (thereby increasing the risk of arterial and venous thrombosis, and thus a higher incidence of myocardial and cerebral infarction), increased blood lipids, migraine headaches, hypertension, uterine fibroid enlargement, fibrocystic breast disease, the appearance of telangiectasias, and carcinogenic effects on the cervix and breast. Side effects due to progestogens include: depression, increased appetite, acne, hirsutism, jaundice, decreased levels of HDL lipoproteins in the blood, cervicitis, and fluid retention. In women with diabetes, hormonal contraceptives may reduce the effectiveness of insulin and other antidiabetic drugs, and increase blood glucose levels, so it is necessary to periodically monitor glycemia.

Contraindications for the use of oral contraception are: pregnancy, vascular disorders and breast or endometrial cancer. Oral contraceptives should not be given to women in the first two years after the first menstruation (menarche) because menstrual cycle disorders may occur after cessation of use and a slightly higher incidence of sterility than in the general population. Also, women older than 40 years should not take these drugs due to the high risk of thrombosis (venous thrombosis, myocardial or cerebral infarction) and hypertension. The risk is especially high in women who smoke.

A special type of oral contraception is postcoital contraception. In the first 72 hours after coitus, conception can be prevented by administering high doses of estrogen (e.g. ethinyl estradiol, 2.5 mg/12 hours, for 5 days) or progestogen (e.g. levonorgestrel, 0.75 mg postcoital). This is of great importance in cases of unwanted conception due to rape or other circumstances.

Table 21. Examples of oral contraceptives.

DRUG	COMMENT	ADMINISTRATION
Norethisterone (0.5 mg) + ethinyl estradiol (0.035 mg)	Combination of gestagen and estrogen	1 tablet/day Fro, 7. to 28. day of menstrual cycle
Levonorgestrel	Progestagen	1 tablet 0.75 mg postcoital

ANDROGEN AND ANABOLIC STEROIDS

The main natural androgen in the human body is testosterone, which is secreted in the testes and (in very small amounts) in the adrenal cortex. The other two natural androgens, dehydroepiandrosterone and androstenedione, are produced primarily in the adrenal cortex; they are significantly less potent than testosterone.

Like other steroid hormones, androgens bind to their intracellular receptors, and the androgen-receptor complex then regulates gene expression in the cell. In some tissues (prostate, hair follicles, seminal vesicles, and epididymis), the active metabolite of testosterone, 5α-dihydrotestosterone, binds to the androgen receptor.

Androgens influence the development of secondary male characteristics (hairiness, deepening of the voice, alopecia, muscularity...), promote the incorporation of amino acids into striated muscle (leading to a positive nitrogen balance) and stimulate the formation of erythrocytes.

Androgens are used in the replacement therapy of hypogonadism in men and for the treatment of delayed puberty in male children. In postmenopausal women, they can be used for the short-term treatment of reduced sexual desire. Testosterone is administered intramuscularly as testosterone enanthate or cypionate, or transdermally using special patches.

Interestingly, low blood testosterone levels are associated with a higher incidence of atrial fibrillation, coronary artery disease, higher mortality from coronary artery disease, worsening heart failure, and a higher incidence of type 2 diabetes. However, testosterone is not approved as a treatment for any of these conditions.

Since androgens cause masculinization in women (deepening of the voice, muscularity, hirsutism, etc.), several compounds have been synthesized that promote the incorporation of amino acids into the muscles and stimulate erythropoiesis as well as natural androgens, but to a much lesser extent they cause masculinization. Such compounds are called anabolic steroids (such as: **oxandrolone, nandrolone, stanozolol, ethyl-estrenol**, etc.). **Anabolic steroids** are used to treat cachexia, to stimulate erythropoiesis in bone marrow failure, and to treat congenital angioneurotic edema. Unfortunately, anabolic steroids are widely abused to increase muscle mass and muscle contraction strength, in order to achieve better results in sports. This phenomenon, called **doping**, is accompanied by undesirable and toxic effects of anabolic steroids, which are dose-dependent (higher doses produce more frequent and severe disorders):

- masculinization in women,
- hypertension,
- increased tendency to thrombosis,
- erythrocythemia,
- cholestatic hepatitis,
- liver tumors,
- decrease in HDL lipoproteins,
- acne on the skin,
- gynecomastia,
- hypogonadism,
- aggressive behavior accompanied by narcissism,
- depression, anxiety, suicidal tendencies, and
- sodium retention.

Table 22. Dose of androgens and anabolic steroids

DRUG	ROUTE OF ADMINIST RATION	DOSE	DOSE INTERVAL	INDICATION
Testosterone	i.m.	25 mg	3 days	Supplementation
Stanozolol	Oral	2 mg	12 h	Congenital angioedema
Nandrolone-decanoate	i.m.	25 mg	1 month	Cahexia

ANTIANDROGENS

Blockade of androgen action is most easily achieved by blocking their receptors or by blocking the formation of the active form of testosterone: 5alpha-dihydrotestosterone.

The first drug that was shown to be able to block androgen receptors was spironolactone (which also blocks aldosterone receptors). Later, cyproterone acetate was discovered, and then flutamide. Today, we have three first-line effective androgen receptor blockers: **flutamide, bicalutamide, and nilutamide**. All three of these drugs are used successfully in the treatment of hirsutism and advanced androgen-dependent prostate cancer. Side effects of flutamide and bicalutamide are not very common; the most serious is the occurrence of toxic hepatitis, which is reversible. Gynecomastia can also occur. After the first generation of androgen receptor blockers, the second generation appeared, consisting of **enzalutamide, apalutamide and darolutamide**. First-generation androgen receptor blockers lose their blocking effect after a certain time because prostate cancer cells produce large amounts of androgen receptors due to mutations, and the tumor begins to produce androgens on its own. Unlike first-generation blockers, second-generation androgen receptor blockers have greater specificity and higher affinity for receptors, which is why they do not lose their blocking effect even in castration-resistant prostate cancer.

Since it was previously observed that one of the antifungal drugs, ketoconazole, can reduce androgen synthesis in the adrenal gland by inhibiting cytochrome CYP17, but weakly, pharmaceutical companies have been working on a large number of new substances that could have the same effect. This led to the development of **abiraterone acetate**, which, due to CYP17 inhibition, reduces androgen synthesis throughout the body, including the adrenal gland and testes, and is therefore very effective in the treatment of locally advanced or metastatic prostate cancer. Since it also disrupts the synthesis of other adrenal hormones to some extent, abiraterone acetate has hypokalemia, fluid retention, and hypertension as side effects, and is therefore only used in combination with prednisone.

Finasteride successfully inhibits the enzyme 5α-reductase, which converts testosterone to 5α-dihydrotestosterone. Given that 5α-dihydrotestosterone is important for androgenic effects in the prostate and hair follicles, it is not surprising that finasteride has found use in the treatment of prostate adenoma (prostatic hypertrophy) and in the treatment of hirsutism. While finasteride is very effective in the treatment of prostate adenoma, when it comes to hirsutism, it is less effective than flutamide. In addition, when finasteride is used in women, it can lead to menstrual cycle disorders. The dosage of finasteride in the treatment of prostate adenoma is 5 mg/day, orally. Finasteride is the only drug that can change the course of benign prostatic hypertrophy and reduce the volume of the gland, but it takes several weeks and months for the effect to be seen.

TREATMENT OF BENIGN PROSTATE HYPERPLASIA

Before prostate hyperplasia becomes so large that it causes complications (urinary retention, bleeding), it can be successfully treated with a combination of alpha-blockers and 5-alpha reductase blockers. Alpha-blockers work immediately by relaxing the internal urethral sphincter and the smooth muscles of the prostate, making urination easier (urine flow improves). The following alpha-blockers are most commonly used for this indication: **doxazosin, alfluzosin, indoramin, prazosin, terazosin and tamsulosin**. They must be administered with caution: the first dose is given at bedtime, in order to avoid the consequences of very pronounced hypotension; later the body gets used to the alpha-blocker, but orthostatic hypotension can occasionally occur, especially when standing up suddenly. In addition to hypotension, alpha-blockers can cause drowsiness, depression, headache, blurred vision, erectile dysfunction, and edema (due to fluid retention due to reduced blood flow through the kidneys).

Finasteride inhibits 5alpha-reductase, an enzyme that converts testosterone to dihydrotestosterone. In the prostate, dihydrotestosterone is much more active than testosterone itself, and leads to hyperplasia. The use of finasteride can achieve prostate reduction within a few months, and thus relieve symptoms (difficulty urinating).

Finasteride is administered at a dose of 5 mg/day, orally. Due to the disruption of normal testosterone metabolism, finasteride has significant side effects: impotence, ejaculation disorders, gynecomastia, decreased libido.

The third group of drugs that can be used in the treatment of benign prostatic hypertrophy are **phosphodiesterase type 5 inhibitors**, which are otherwise used to treat erectile dysfunction. They reduce the muscle tone of the bladder, prostate, and urethra, making urination easier. They are less effective than alpha-blockers, but can be combined with them. The most commonly used drug in this group is **tadalafil**. The main side effects are headache and worsening of coronary artery disease and heart failure, especially if used simultaneously with nitrates.

TREATMENT OF IMPOTENCE

Impotence is the inability to achieve a penile erection sufficient for satisfactory coitus for a period longer than 6 months. The cause of impotence can be psychological, hormonal (lack of androgen hormones, increased production of female sex hormones), arterial (arteriosclerosis of the arteries of the penis), cavernous (fibrosis of the cavernous bodies) or neurogenic (damage to the reflex arc necessary for erection or to higher structures that control the activity of the reflex arc). Regardless of the cause, impotence can be successfully treated with several drugs:

1. **Prostaglandin E1 (alprostadil)** can be injected into the cavernous bodies or applied transurethrally, in the form of a cream. In both cases, alprostadil causes vasodilation and relaxation of the cavernous bodies, which allows for a rapid influx of blood and slow swelling, i.e., erection. Erection occurs regardless of the presence or absence of sexual arousal, and lasts 20-60 minutes. During this time, penetration is possible. The disadvantages of this therapy are complicated administration, the appearance of hematomas on the penis, priapism (prolonged and painful erection, over 6 hours) and, sometimes, the appearance of fibrosis of the cavernous bodies.
2. **Sildenafil** (a product of the Pfizer company under the name Viagra) is a selective inhibitor of phosphodiesterase type 5, which is found in the tissues of the penis. Due to this inhibition, there is an accumulation of cyclic guanosine monophosphate, but only if the release of nitric oxide (NO) from the nerve structures of the penis is increased as a result of sexual arousal (NO stimulates guanylate cyclase and increases the formation of cGMP). The accumulation of cGMP leads to relaxation of the corpus cavernosum, which allows a sudden influx of blood and results in an erection. To achieve the desired effect, a 50 mg tablet should be taken one hour before coitus. The half-life of sildenafil is 3-5 hours. Side effects of sildenafil include color vision disorders, headache, flushing, and hypotension. Concomitant use of sildenafil with nitrates or other vasodilators ***is contraindicated*** because it may cause extreme hypotension, decreased coronary artery perfusion, and myocardial infarction.
3. In addition to sildenafil, three other phosphodiesterase type 5 blockers have come into use: **tadalafil, vardenafil, and avanafil**. While vardenafil is very similar to sildenafil in all respects, tadalafil is characterized by slow absorption from the digestive tract, but also by a longer duration of action. While the effects of sildenafil and vardenafil last for several hours, tadalafil is still effective 36 hours after the dose. Avanafil is more selective than the others, so it is equally effective, and has fewer side effects.
4. **Apomorphine** has recently been used to treat impotence. It is administered as a sublingual tablet, 2 mg about 20 minutes before sexual activity. The next dose of apomorphine can only be administered after more than 8 hours have passed. Like the other two drugs for impotence, apomorphine increases blood flow to the cavernous bodies of the penis. Apomorphine causes vasodilation and hypotension, so it should be avoided in people with heart failure or coronary disease, as it may worsen it. The vaso-vagal syndrome that apomorphine sometimes provokes is also very unpleasant: sweating and syncope.

MELATONIN

Melatonin is a hormone of the pineal gland. Its chemical composition is methylated and acetylated serotonin. Its secretion is inhibited during wakefulness by the tonic activity of the retino-hypothalamic tract. During the night, when the activity of this pathway decreases, melatonin secretion increases significantly. In lower animals, melatonin can change the color of the skin and thus enable adaptation to living conditions with less light. In humans, melatonin facilitates the normal shift between wakefulness and sleep, and also has a general hypnotic effect. Therefore, it is used therapeutically to establish a normal wakefulness-sleep rhythm in people who have suddenly changed time zones (e.g., after a flight from Europe to America there is so-called "jet lag", so the passenger cannot fall asleep at night) or who are forced to work the night shift. There is increasing evidence of the immunostimulatory and antioxidant role of melatonin, and its usefulness in the treatment of infections, inflammatory diseases, cardiovascular diseases, obesity, neurodegenerative diseases, and others, but melatonin still has only one approved indication – the treatment of jet lag.

Melatonin is also used to treat insomnia that is not related to a disruption of the circadian rhythm of light exposure. It successfully prolongs sleep, facilitates falling asleep, and increases the quality of sleep, so that the patient is more rested upon awakening.

The side effects of melatonin are relatively mild: drowsiness the next day, malaise, headache, and tachycardia.

GHRELIN

Ghrelin is a peptide hormone secreted by the stomach in response to starvation. Ghrelin acts on the hypothalamus to increase the amount of **agouti-related peptide and neuropeptide Y** (these are mediators that increase hunger and appetite). In addition, ghrelin increases the secretion of growth hormone from the pituitary gland through the hypothalamus. Since ghrelin, in summary, leads to an increase in appetite and greater food intake, and also has anti-inflammatory effects, it has great potential for the treatment of cachexia in chronic diseases. A few years ago, a ghrelin analog **anamorelin**, which is administered orally, was approved in Japan for the treatment of cachexia in cancer. Anamorelin successfully eliminates cachexia that is mild to moderate, while it is less effective in the most severe forms. It is necessary that the patient increases food intake and has some physical activity in order for anamorelin to work. The most serious side effect of anamorelin is ventricular arrhythmias.

MEGESTROL

Megestrol is a progesterone analogue whose exact mechanism of action is unknown, but it has been used off-label for several decades (it is approved only for the treatment of hormone-dependent breast cancer) to treat cachexia and anorexia in patients with acquired immunodeficiency syndrome or malignant tumors. Its efficacy has recently been questioned after a systematic review of published clinical studies. Among the side effects of megestrol, thromboembolism, transient adrenal insufficiency, hypogonadism, edema, and confusion are possible.

CONTROL OF CALCIUM AND PHOSPHORUS METABOLISM

Calcium and phosphorus in the form of phosphates are necessary for most metabolic processes, for the secretion of exocrine and endocrine glands, for the contraction of smooth and striated muscles, and for bone mineralization. Both calcium and phosphates are absorbed in the small intestine and excreted by filtration in the kidneys. Vitamin D in its active form (1,25-dihydroxy-cholecalciferol) increases the absorption of calcium and phosphate in the intestines and their reabsorption in the renal tubules. This ensures optimal levels of calcium and phosphate in the blood, necessary for normal bone mineralization. Parathormone (parathyroid hormone) increases the activity of osteoclasts, i.e., increases bone resorption and facilitates the conversion of vitamin D into its active form in the kidney. In addition, this hormone increases calcium reabsorption and inhibits phosphate reabsorption in the renal tubules. The final effect of PTH action is an increase in blood calcium concentration and a decrease in phosphate concentration.

Calcium is found in the blood bound to plasma proteins (about 50%), in association with organic anions (3%, citrate, lactate) and free, ionized (about 47%; this is the active form of calcium). The total concentration of calcium in the blood is about 2.5 mM/L and that of phosphate is about 1 mM/L.

A decreased level of calcium in the blood (hypocalcemia) leads to the appearance of spasms of the striated muscles (tetany). An extension of the QT interval can be seen on the ECG. Severe hypocalcemia is treated with slow intravenous administration (over 20 minutes) of calcium gluconate (10 ml of a 10% solution) or calcium chloride. On the other hand, chronic calcium replacement is done with oral administration of calcium carbonate (1-2 g daily). Hypercalcemia (very common in generalized malignant diseases) primarily affects the functioning of the CNS. Confusion occurs first, followed by somnolence, stupor, and coma. The QT interval is shortened on the ECG. Hypercalcemia is primarily treated with loop diuretics in combination with saline infusions (0.9% NaCl 4L/24 hours + 125 mg furosemide i.v.). Calcitonin, a thyroid C-cell hormone that inhibits osteoclast activity, can also be administered (dose: 8 IU/kg/8 hours i.m.).

Vitamin D exists in two forms: cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Cholesterol is oxidized in the intestinal epithelium to 7-dehydrocholesterol; dehydrocholesterol is converted to cholecalciferol in the skin under the influence of UV light. Ergocalciferol is part of the cell membranes of plants and is ingested with food. Both cholecalciferol and ergocalciferol are then hydroxylated first in the liver at position 25 and then in the kidney at position 1. The resulting 1,25-dihydroxy derivatives represent the active forms of vitamin D.

Due to a lack of vitamin D, defective bone mineralization occurs, which manifests itself in rickets in children and osteomalacia in adults. Therefore, vitamin D is given to children in the first two years of life prophylactically, in order to prevent the occurrence of rickets. The daily dose is 400 IU. In significantly higher doses, vitamin D can be used to treat rickets and osteomalacia.

During chronic renal failure, 1-hydroxylation of 25-OH-derivatives of vitamin D is disabled, resulting in a deficiency of the active form of the vitamin and defective bone mineralization - the so-called renal osteodystrophy. **Calcitriol** (1,25-(OH)2-vitamin D) or **1-alpha-calcidiol** (a synthetic analogue of vitamin D that is hydroxylated at the 1alpha position, and after additional 25-hydroxylation in the liver it becomes active), is used for its treatment, because both of these forms do not need to be hydroxylated in the kidney. The calcitriol derivative **paricalcitol** (19-nor-1,25-dihydroxy vitamin D2) is even more effective than calcitriol in the treatment of renal osteodystrophy, because it lowers the concentration of parathyroid hormone in the blood more quickly, disrupts serum calcium and phosphate levels less, and is also effective in patients with high serum phosphate concentrations. It has also been shown that the survival of patients receiving paricalcitol is longer than the survival of patients treated with calcitriol. **Takalcitol** (1α,24(OH)2D3) is a vitamin D derivative used to treat psoriasis.

In case of overdose, vitamin D is toxic (hypervitaminosis D). Hypercalcemia and hypercalciuria occur.

Hypoparathyroidism most often occurs after surgical removal of the thyroid gland, when the parathyroid glands are also removed. Hypocalcemia occurs, which is treated with calcium and vitamin D preparations (50,000 IU of vitamin D, 3 times a week + 1g of CaCO3/day). Hyperparathyroidism is treated surgically - by removing the tumor or hyperplasia of the parathyroid gland.

Osteoporosis is the loss of bone mass: both the bone matrix and the minerals together. It occurs in old age, in women after menopause, and after long-term use of corticosteroids. It causes an increased incidence of fractures and bone pain. Osteoporosis drugs can be classified into three groups: (1) drugs that reduce bone breakdown (bisphosphonates, denosumab), (2) drugs that increase both breakdown and bone formation, i.e., bone remodeling stimulants (teriparatide and abaloparatide), and (3) drugs that reduce breakdown and increase bone formation (romosozumab).

Although **calcitonin** (which inhibits osteoclast activity) can also be used to treat osteoporosis, bisphosphonates are currently more effective. Bisphosphonates are pyrophosphate analogues that have a carbon atom instead of oxygen: -R-C-R- instead of -R-O-R-. They are deposited in the bones, stabilize hydroxyapatite, and prevent bone resorption. Thus, the processes of synthesis overcome the processes of resorption, and osteoporosis improves**. Etidronate, pamidronate, alendronate, ibandronate, zoledronate**, and other bisphosphonates have proven to be very successful in the treatment and prevention of osteoporosis with very few side effects. Zolendronate is also very useful in preventing pathological fractures in bone metastases, e.g. after prostate cancer, as well as in the treatment of hypercalcemia in advanced cancers. However, if overdosed, they can lead to bone demineralization and loss of dental implants. Also, orally administered bisphosphonates are irritating to the esophageal mucosa, so they must be taken with plenty of water, and the patient should remain upright for at least 1 hour after swallowing the tablet. When bisphosphonates are administered parenterally (e.g. pamidronate, zolendronate or ibandronate), they show nephrotoxic effects in 5-10% of patients. The nephrotoxic effect can be partially avoided if the patient is well hydrated.

Osteoporosis in Postmenopausal bleeding can also be successfully stopped by using estrogen (e.g. 25 mcg of ethinyl estradiol daily) or raloxifene for several years. To reduce the risk of endometrial cancer, a progestogen (e.g. 2.5 mg of medroxyprogesterone daily) is also used at the same time.

Today, we have a very effective osteoporosis drug available, which we use when bisphosphonates no longer work. It is **denosumab**, a monoclonal antibody against the RANKL factor (receptor activator of nuclear factor kappa B ligand), which, by neutralizing the aforementioned factor, leads to reduced osteoclast activity. RANKL stimulates the proliferation and activity of osteoclasts. Denosumab is administered subcutaneously, once every 6 months. It has shown greater efficacy than bisphosphonates in the treatment of osteoporosis in postmenopausal women (it stops osteoporosis and reduces the risk of fractures). The drug is well tolerated, but it has been observed that in a small number of patients the risk of skin and subcutaneous tissue infections increases, and osteonecrosis of the jaw may also occur.

The group of drugs that increase both bone breakdown and formation include **teriparatide and abaloparatide**. Teriparatide is the active fragment (1-34) of parathyroid hormone, which directly stimulates osteoblast activity in the bones, and indirectly increases calcium absorption in the intestines, and calcium reabsorption and phosphate excretion in the renal tubules. It is the only drug that can not only stop osteoporosis, but also increase bone density. It significantly reduces the incidence of vertebral fractures, but not femoral fractures. Teriparatide is administered subcutaneously, once a day. Among the side effects, the drug causes pain in the extremities, anemia, depression and hypotension. Abaloparatide is a peptide analogue of a human protein that is similar to parathyroid hormone. The effect of abaloparatide is reflected in an increase in bone density. Abaloparatide is more effective than teriparatide in preventing bone fractures in severe osteoporosis. The main side effect of this drug is hypercalcemia with accompanying hypercalciuria.

The most effective osteoporosis drug today is **romosozumab**, a humanized monoclonal antibody that blocks the action of **sclerostin**. Sclerostin is a signaling protein produced by osteocytes and chondrocytes that inhibits osteoblast activity. Romosozumab removes the inhibitory effect of sclerostin, so osteoblasts create new bone. In addition, romosozumab reduces the expression of osteoclast stimulators, thereby reducing bone resorption. It is administered as a subcutaneous injection once a month. After two years of use, the relative reduction in the risk of vertebral fractures is about 50%. It is contraindicated in people who have had a myocardial infarction or stroke. It can cause hypocalcemia.

PHARMACOLOGY OF BLOOD AND TISSUES

ANTICOAGULANT THERAPY

Normal blood coagulability is necessary for maintaining blood in the blood vessels and the heart. Sometimes there is inadequate and excessive activation of the coagulation system and the formation of a thrombus inside the blood vessels. A thrombus is made up of a fibrin network in which blood cells are trapped: primarily platelets, then erythrocytes and leukocytes. A thrombus in arteries (in which blood flow is fast) consists mainly of fibrin and platelets (the so-called white thrombus), and a thrombus in veins also has many erythrocytes (red thrombus).

Drugs that can reduce blood coagulability can also prevent the formation of a thrombus.

Oral anticoagulants – vitamin K inhibitors. These are drugs that inhibit the reduction of vitamin K in the liver. Reduced vitamin K is necessary for the carboxylation of coagulation factors 2, 7, 9 and 10, as well as anticoagulant protein C, which are synthesized in the liver. Factors that are not carboxylated cannot participate in the coagulation process, and thus the formation of a new thrombus is prevented.

All oral anticoagulants that inhibit vitamin K are either coumarin derivatives (**warfarin, acenocoumarol**) or indanedione derivatives (phenindione). Indanedione derivatives are as effective as coumarin derivatives, but significantly more toxic; therefore, coumarin derivatives have an advantage in practice. They are well absorbed from the digestive tract, penetrate all tissues, are metabolized in the liver, and the metabolites are excreted in the urine. They cross the placenta and are **teratogenic**; therefore, they are not used during pregnancy. From the beginning of administration to the beginning of action, 1-3 days must pass, which is how long it takes for the already synthesized coagulation factors in the blood to be consumed. During this time, the patient can be protected with heparin, which is discontinued after the onset of action of oral anticoagulants.

Warfarin (a racemic mixture of S- and R- enantiomers) is highly bound to plasma proteins (more than 95%), which creates the possibility of interactions with other drugs that are also bound to plasma proteins. In the liver, warfarin is metabolized under the action of cytochrome P450, namely isoforms 2C9 and 1A2, and its metabolites are excreted in the bile. Warfarin (and other anticoagulants) interacts with a large number of drugs that either induce or inhibit the activity of the aforementioned forms of cytochrome. Therefore, when prescribing other medications to patients on chronic oral anticoagulant therapy, a physician should always consult the reference literature, check for possible interactions, and adjust the dosage of the medications accordingly.

Oral anticoagulants, vitamin K inhibitors, are used to treat deep vein thrombosis, to prevent and treat pulmonary embolism, to prevent thrombosis after implantation of artificial heart valves, and to prevent thrombosis in heart aneurysms. Oral anticoagulants can also be used to prevent thromboembolic complications in atrial fibrillation due to mitral stenosis or some myocardial disease. Oral anticoagulants do not affect already formed thrombi. Oral anticoagulants, vitamin K inhibitors, are dosed individually, based on the control of prothrombin time. The effect of oral anticoagulants on prothrombin time is currently expressed through INR (International Normalized Ratio). This is the ratio of the prothrombin time of the patient and the control, both times being obtained using an international reference thromboplastin made from human brain, and not, as before, from rabbit brain. The optimal effect of oral anticoagulants is achieved if the INR is in the range of **2.5 to 3.5**.

If oral anticoagulants are overdosed, the **antidote - vitamin K** - should be administered. Coagulation normalization occurs 12 to 24 hours after its administration. If it is necessary to normalize coagulation urgently (e.g. in case of severe bleeding), this can be done by administering **fresh plasma or coagulation factor concentrates**.

Adverse effects include: gastrointestinal and CNS bleeding, subcutaneous vein thrombosis with fatty tissue necrosis (in the breast and gluteal region, due to decreased plasma protein C activity) and, rarely, liver damage. Subcutaneous vein thrombosis occurs at the very beginning of therapy (in the first 2-3 days), while the anticoagulant effect has not yet been established. Diarrhea, alopecia, necrosis of the small intestine and livid toes are rare. Oral anticoagulants, vitamin K inhibitors, are contraindicated in all conditions where there is an increased risk of bleeding with serious consequences: if there is a peptic ulcer, in malignant hypertension, bacterial endocarditis, thrombocytopenia and similar conditions.

Heparin. Heparin is a mixture of complex carbohydrates from the glycosaminoglycan group. These are natural substances that can be found in the granules of mast cells, basophils and other mucosal cells. Heparin binds to antithrombin 3 and increases its inhibitory effect on thrombin, factors 10 and 9 of the coagulation system. Heparin also increases the inhibitory effect of cofactor 2 on thrombin. Its action begins immediately after administration.

Parenteral administration of heparin is allowed only by intravenous or subcutaneous route; intramuscular injection is avoided, as it may cause hematoma formation at the site of administration.

Heparin is partly metabolized in the liver (in the reticuloendothelial system), and partly eliminated unchanged by the kidneys (T1/2 is about 90 minutes).

Heparin is used for the treatment and prevention of deep vein thrombosis and as a prophylaxis of thrombosis of vascular grafts after their implantation. In addition, it is used in the prophylaxis and treatment of embolism, in the prevention of postoperative venous thrombosis and as an additional agent in the treatment of myocardial infarction. Together with antiplatelet drugs, heparin reduces the rate of myocardial infarction in patients with unstable angina pectoris, as well as the rate of occlusion of bypass grafts and coronary arteries after percutaneous interventions (stents or angioplasty).

If anticoagulant therapy is required for a longer period, then oral anticoagulants should be switched to soon after the introduction of heparin. Oral anticoagulants are usually started at the same time as heparin; as soon as they start to take effect, heparin is stopped. Heparin should not be given for more than 7 days because side effects are more likely to occur.

If heparin is used therapeutically, the dose is 5-10,000 IU/6 hours intravenously. For the prophylaxis of deep vein thrombosis (for example, after major surgery), it is administered subcutaneously, at a dose of 5,000 IU/12 hours. The dose of heparin is adjusted according to the value of the activated partial thromboplastin time (aPTT); aPTT should be 1.5 - 2 times longer than in a person not receiving heparin.

If heparin is overdosed, bleeding can be avoided (or stopped, if it has already started) by administering the antidote – **protamine sulfate**, which binds to heparin through ionic bonds and inactivates it. For every 100 IU of heparin administered, 1 mg of protamine sulfate should be given.

The most common adverse effects of heparin are bleeding and thrombocytopenia. Thrombocytopenia occurs in about 5-30% of patients, and can be "early" and "delayed". "Early" thrombocytopenia occurs immediately after heparin administration, and is transient. "Delayed" thrombocytopenia is the result of the formation of antibodies to platelets whose effect depends on heparin, so that platelets are destroyed by the action of the antibodies. Delayed thrombocytopenia is accompanied by thrombosis of small arteries and subsequent gangrene of the fingertips. These thrombosis are treated with drugs that directly inhibit thrombin: **argatroban and bivalirudin**. In addition to the two adverse effects already mentioned, heparin can cause fever, alopecia, osteoporosis, bone pain and hypoaldosteronism. As with oral anticoagulants, heparin should not be given in conditions in which there is a tendency to bleed with serious consequences.

Since heparin does not cross the placental barrier, it can be used during pregnancy.

Since the 5-amino-sugar sequence is essential for the action of heparin, substances containing this sequence have been synthesized, whose molecules are significantly shorter than the heparin molecule. These are the so-called **low-molecular-weight heparins**. Unlike true heparin, they inhibit the action of only factor X, and not other factors. However, their clinical anticoagulant effect is not weaker than that of heparin. On the contrary, they have significant advantages over heparin. They less frequently cause thrombocytopenia and osteoporosis, and after subcutaneous administration their effect lasts longer; due to their more reliable and predictable effect, when these drugs are used, it is not necessary to control aPTT, as with the use of regular heparin. Their effect can only be monitored in highly specialized laboratories, by measuring the level of activated factor Xa.

Low molecular weight heparins have proven to be effective, especially in the prophylaxis of venous thrombosis in orthopedic and other surgeries. Of the low molecular weight heparins**, enoxaparin** was the first to enter clinical practice, and today **dalteparin, reviparin, nadroparin and tinzaparin** are also used. Starting from 20 years ago, low molecular weight heparins (also called 'fractionated') are used for the treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and for the prevention of coagulation in the extracorporeal circulation machine or for hemodialysis. If low molecular weight heparins are overdosed, protamine sulfate can be used as an antidote.

A drug containing only 5 amino sugars is called **fondaparinux**. It directly inhibits factor X, and is used in all indications for which low molecular weight heparins are used: prophylaxis and treatment of deep vein thrombosis and embolism, treatment of unstable angina pectoris and myocardial infarction. It is as effective as other low molecular weight heparins, but unlike them, it rarely causes thrombocytopenia.

New oral anticoagulants

New oral anticoagulants do not act through vitamin K, but through other mechanisms, but are also administered orally. Since they do not require INR monitoring, their administration is simpler for patients, and the risk of bleeding is similar to that of warfarin.

Dabigatran etexilate is a direct thrombin inhibitor that can be taken orally. It is as effective as low-molecular-weight heparins in preventing deep vein thrombosis; monitoring of coagulation tests is not required when using dabigatran. The only significant side effect of this drug is bleeding. Dabigatran is also used for the prevention of stroke and embolism in atrial fibrillation, as well as for the treatment of deep vein thrombosis and pulmonary embolism. Dabigatran is largely excreted

unchanged in the urine. In case of severe bleeding due to dabigatran, the antidote **idarucizumab** can be used. Idarucizumab is a monoclonal antibody that binds to dabigatran after intravenous administration, thus interrupting its action.

Rivaroxaban, apixaban, and edoxaban are direct factor X inhibitors used for the prevention of deep vein thrombosis in orthopedic surgery, for the prevention of embolization in patients with atrial fibrillation not caused by heart valve disease, and for the treatment of deep vein thrombosis and pulmonary embolism. They can be taken orally. They are as effective as dabigatran and low-molecular-weight heparins. They do not require monitoring of coagulation tests. The most important side effect of these drugs is bleeding. Rivaroxaban and apixaban are metabolized primarily in the liver by cytochromes, but also by other pathways to inactive metabolites. Edoxaban is also metabolized in the liver, but predominantly by hydrolysis outside the cytochrome. Edoxaban is a substrate for the efflux pump, P-glycoprotein, and interacts with other drugs that can inhibit this pump. If severe bleeding occurs due to the use of rivaroxaban, apixaban, or edoxaban, the antidote **andexanet alfa** can be administered. Andexanet is a genetically modified FXa that binds to rivaroxaban and apixaban after intravenous administration, thus interrupting their action.

Hirudin and drugs derived from it. The anticoagulant hirudin is a component of the saliva of the leech (Hirudo medicinalis). By directly binding to thrombin, it inhibits its action; thus preventing the formation of fibrin, or thrombus. Hirudin is not used as a drug, but its analogues are in use: **lepirudin, argatroban and bivalirudin**. They reversibly inhibit thrombin, both in the circulation and in the thrombus. They prolong prothrombin time, thrombin time and activated partial thromboplastin time. Bivalirudin and the other two direct thrombin inhibitors are indicated for reducing blood coagulability in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. They are administered together with aspirin. For this indication, they have shown greater efficacy than heparin. They are also used to treat venous thromboses associated with heparin-induced thrombocytopenia.

The main risk of these drugs is bleeding; however, bleeding is less common than with heparin.

Bivalirudin is administered intravenously. The effect begins immediately after administration and ends 1 hour after discontinuation of administration. The drug is removed from the circulation by the action of peptidases and filtration in the kidneys. Argatroban is broken down in the liver.

Table 23. Usual doses of oral anticoagulants and low molecular weight heparins.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Varfarin	Oral	5 mg	24 h
Enoxaparin	Subcutaneous	2000 IJ	24 h

VITAMIN K

Fat-soluble vitamin K exists in two forms: **phylloquinone** (**phytomenadione, vitamin K1**), which is found in green leafy vegetables, and **menaquinone (vitamin K2**), which is synthesized by bacteria in the colon. It is first reduced in the liver and as such catalyzes the carboxylation of coagulation factors 2, 7, 9 and 10. Carboxylation of these factors is necessary for their normal function in the coagulation process.

The daily requirement for vitamin K is about 1 mcg/kg. There is a depot of this vitamin in the liver that lasts only a few weeks in the event of complete cessation of intake.

Vitamin K is used for: 1) treatment of overdose of oral anticoagulants; 2) treatment of coagulation disorders during obstructive jaundice; 3) prevention of hemorrhagic disease of the newborn (the newborn does not yet have enough bacteria in the colon to produce vitamin K; therefore, each newborn is given 1 mg of this vitamin i.m.); 4) treatment of vitamin K deficiency (with long-term use of antibiotics that sterilize the colon, in malabsorption).

Intravenous administration of vitamin K1 may be accompanied by mast cell degranulation: hypotension, dyspnea, chest and back pain occur. Therefore, i.v. administration of vitamin K1 is carried out in the form of intravenous infusion (the drug is diluted with 5% glucose, the infusion system must be dark in color, and the infusion bottle must be protected from light, because vitamin K decomposes in light).

Synthetic vitamin K (menadione, vitamin K3), which is water-soluble, must first be converted to vitamin K1 in the liver to be effective. Therefore, it should be avoided in practice - for example, in overdoses of oral anticoagulants, menadione is ineffective.

IRON

Iron is found in large quantities in green vegetables and "red" animal meat, in the divalent (Fe2+) or trivalent (Fe3+) form. In the stomach, under the action of hydrochloric acid, trivalent iron is converted to the divalent form (Fe2+), which is much better absorbed in the duodenum and small intestine. Absorption is carried out by a specific transport system in the enterocyte membrane. From the enterocyte, iron is transported to other tissues bound to the plasma protein, **transferrin**. Iron in the divalent form (Fe2+) is a component of heme in hemoglobin and myoglobin, and the cytochromes of all cells. It is necessary for oxygen transport and cellular respiration. Excess iron (especially in the liver) is bound to the intracellular protein **ferritin**; In case of excessive iron accumulation, ferritin molecules aggregate into a complex known as **hemosiderin**.

Elimination of iron from the human body is carried out only by exfoliation of dead cells from the skin and mucous membranes of the digestive and respiratory tract. Therefore, iron accumulates very easily in the body with excessive intake. Daily iron requirements are about 1 mg.

Iron deficiency manifests itself as hypochromic microcytic anemia. Usually, the deficiency occurs due to chronic loss of small amounts of blood (in women during menstruation, in men, e.g. from hemorrhoids), and less often due to insufficient intake.

Iron deficiency in the body can be assessed based on measuring the concentration of hemoglobin in the blood, because it is known that 1L of blood (140g of hemoglobin) contains about **470 mg** of iron. If a patient, e.g., has only 100 g of hemoglobin per liter of blood, which means he lacks:

$$\frac{140-100}{140}\cdot 470mg$$

of iron per liter of blood. Since a person has about 5L of blood, the resulting amount should be multiplied by 5 and about 500 mg added to replenish depleted depots.

Iron can be administered orally (usually as **FeSO4**) or intravenously (as **Fe-dextran, iron(III) - hydroxide sucrose complex, iron(III) isomaltoside, ferumoxytol, sodium iron(III) gluconate**). Oral administration is simpler, but is associated with irritation of the gastric and small intestinal mucosa. It should also be borne in mind that about 10% of the amount of iron ingested orally is absorbed. Intravenous administration can provide the total amount of iron that is missing at once, but a number of people (about 1%) may react with fever, nausea, back pain, facial flushing, or bronchospasm. Therefore, a small test dose (20 mg of iron) is always given first for 30 minutes, and if there is no reaction, the entire amount is continued by slow intravenous infusion.

In practice, the use of **iron (III) carboxymaltose** for intravenous iron replacement should be **avoided**, because every second patient treated with this preparation develops hypophosphatemia, which then leads to osteomalacia, sometimes permanent. This complication is also called the "**6H syndrome**" (elevated FGF-23, hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism). Other intravenous iron compounds can also cause hypophosphatemia, but the incidence is less than 10%.

Acute iron poisoning

Acute iron poisoning is common in young children who usually swallow their mothers' red-colored iron tablets, thinking they are candy. Poisoning occurs in **three stages**. Initially, about 60 minutes after taking the tablets, **diarrhea, hematemesis, and melena** occur. Then there is a **slight improvement** (stage 2), followed by damage to the **central nervous system** with epileptic seizures and coma. Finally, **liver failure** can occur (stage 3). Sometimes the fourth stage of poisoning is considered to be **ileus**, which can occur weeks after the poison is ingested due to cicatricial stenosis of the small intestine.

In addition to general measures (rehydration, shock control, nursing), patients are treated with oral (to prevent further iron absorption) and parenteral administration of deferioxamine chelate.

VITAMIN B_{12} AND FOLIC ACID

Vitamin B12 exists in nature as hydroxy- or cyano-cobalamin. Folic acid is reduced in the human body to its active form - tetrahydrofolic acid. Both vitamin B12 and tetrahydrofolic acid play the role of methyl group carriers in many reactions, primarily

in the synthesis of purine bases and thymidylate. In addition, vitamin B12 is necessary for the regeneration of tetrahydrofolic acid from methyl-tetrahydrofolate. Vitamin B12 is also a cofactor in a key reaction in the synthesis of fatty acids: the conversion of methylmalonyl-CoA to succinyl-CoA; due to a lack of vitamin B12, abnormal fatty acids are formed that are incorporated into the membranes of nerve cells.

Vitamin B12 is abundant in animal liver and eggs. In order to be absorbed in the ileum, it must first bind to a glycoprotein produced by the gastric mucosa called "intrinsic factor". Vitamin B12 deficiency usually occurs when the gastric mucosa is damaged (atrophic gastritis) or removed (e.g. total gastrectomy, gastric resection). On the other hand, folic acid is found in green vegetables, yeast, and the liver of animals. Folic acid deficiency occurs due to a deficient diet. The daily requirement for vitamin B12 is about 2 mcg, and the daily requirement for folic acid is about 0.5-1 mg. While vitamin B12 is stored in large quantities in the liver (so that even after complete cessation of intake, it takes about 5 years for a deficiency to appear), the folic acid depot is only about ten milligrams, so that after cessation of intake, symptoms and signs of deficiency appear after just a few days.

Deficiency of both vitamin B12 and folic acid results in impaired synthesis of nucleic acids, which is manifested primarily by the occurrence of megaloblastic anemia. When it comes to vitamin B12, its deficiency, in addition to anemia, also leads to a neurological disorder - funicular myelosis (degeneration of the dorsal columns of the spinal cord).

Vitamin B12 is administered intramuscularly, in a dose of 1 to 2.5 mg, and folic acid is usually administered orally, in a daily dose of 5 mg. Folic acid alone should never be administered in megaloblastic anemia unless vitamin B12 deficiency has been previously ruled out! Otherwise, anemia will heal, and funicular myelosis will worsen!

Folic acid is routinely administered to all pregnant women at a dose of 0.4 - 0.8 mg per day, as it has been shown to reduce the risk of neural tube defects. Higher doses are used in pregnant women taking antiepileptic drugs, especially carbamazepine and valproate, as their children are at increased risk of spina bifida.

Folic acid and vitamin B12 have no side effects, even when administered in high doses. Any excess of the drugs taken is excreted in the urine.

HEMATOLOGICAL GROWTH FACTORS

The growth, proliferation and differentiation of blood lineages in the bone marrow are dependent on protein hormones produced in the kidney (**erythropoietin**) or secreted by lymphocytes (granulocyte-macrophage colony-stimulating factor /GM-CSF/ and granulocyte-colony-stimulating factor /G-CSF/). Erythropoietin stimulates the growth of the erythrocyte lineage, G-CSF (also known as **filgrastim**) stimulates the production of granulocytes, and GM-CSF (also known as **molgramostim**) stimulates the proliferation and differentiation of all blood lineages. The glycosylated form of G-CSF is called **lenograstim**. In order to administer filgrastim not every day, but once a week, a pegylated preparation of filgrastim (filgrastim linked to polyethylene glycol - **pegfilgrastim**) for subcutaneous administration has been produced, which acts as a depot preparation, i.e., gradually releases filgrastim into the bloodstream from the site of administration.

There are two preparations of erythropoietin - erythropoietin alfa and erythropoietin beta. There is no difference between them in terms of efficacy, but erythropoietin alfa can be administered only intravenously, and erythropoietin beta both intravenously and subcutaneously. The administration of erythropoietin alfa subcutaneously has been discontinued due to the occurrence of **pure red cell aplasia syndrome**.

Erythropoietin is used to treat severe anemia in chronic renal failure, and G-CSF and GM-CSF are used to accelerate the recovery of white blood cells in the bone marrow after the use of cytostatics in the treatment of some malignant diseases. All three growth factors can be useful in aplastic anemia and other types of bone marrow failure. The erythropoietin analog, **darbepoetin alpha**, differs from erythropoietin in the number of oligosaccharide chains, but has an identical mechanism of action. The difference in molecular structure allows it to remain in the body longer than erythropoietin, so it is administered once a week, as a subcutaneous injection.

A side effect of erythropoietin can be an ***excessive increase in hematocrit with subsequent hypertension and thrombosis***. G-CSF can cause bone pain, and GM-CSF a flu-like condition with edema and effusions in the pleura and pericardium.

Erythropoietin is abused in elite sports, as a doping agent. It is used especially in endurance sports, e.g. cycling, marathon runners, etc. Several deaths have been reported in athletes who abused it, because an increased number of erythrocytes increases blood viscosity, and thus the tendency to thrombosis and myocardial infarction.

Thrombopoietin receptor agonists are used to stimulate platelet production: **eltrombopag, lusutrombopag, avatrombopag**, and **romiplostim**. The first three drugs listed are substances whose molecule somewhat resembles peptides, while romiplostim is a polypeptide. Eltrombopag, lusutrombopag, and avatrombopag are administered orally, are highly bound to plasma proteins, and are metabolized in the liver by cytochromes. Romiplostim is administered as a subcutaneous injection and is degraded like other

polypeptides in the reticuloendothelial system. Thrombopoietin receptor agonists are used to treat various types of **thrombocytopenia**. Side effects of these drugs include thrombosis, thrombocytosis, and stimulation of the growth of some malignant tumors.

Table 24. Doses of hematological growth factors.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Erythropoietin	i.v., s.c.	100 IJ/kg	3 days
Filgrastim	i.v., s.c.	5 μg/kg	24 h
Molgramostim	i.v.	250 $\mu g/m^2$	24 h

ANTIAGGREGATION DRUGS

In arteries, where the blood flow is very fast, white thrombi are formed, composed only of aggregated platelets. Thrombi usually form at sites where atheromatous plaque ruptures, i.e., where the endothelium bursts and the intima is exposed. Platelet aggregation is assisted and accelerated by thromboxane A2 and adenosine diphosphate (ADP), and is slowed down by cyclic adenosine monophosphate (cAMP). All of these substances are products of the platelets themselves. The act of aggregation itself occurs by binding fibrinogen at one end to glycoprotein IIb/IIIa receptors on platelets, and at the other end to von Willebrand factor in the exposed intima of the blood vessel.

Platelet aggregation can be reduced by drugs that inhibit prostaglandin synthesis in platelets (acetylsalicylic acid), drugs that increase the concentration of cAMP in platelets (dipyridamole), drugs that block ADP receptors (thienopyridines [ticlopidine, prasugrel, and clopidogrel] and ticagrelor), or drugs that bind to and inactivate IIb/IIIa receptors on platelets (abciximab, eptifibatide, and tirofiban).

These drugs are used primarily prophylactically, to prevent thrombosis of the coronary arteries (prevention of myocardial infarction) and cerebral arteries (prevention of cerebral infarction). They also prevent thrombosis after percutaneous interventions on the coronary arteries.

Acetylsalicylic acid exerts its antiaggregatory effect only in small doses (100 mg/day or 300 mg every third day) because higher doses also inhibit the production of the endothelial prostaglandin, prostacyclin, (PG I), which otherwise has antiaggregatory and vasodilator effects.

The efficacy of aspirin, dipyridamole, clopidogrel, prasugrel and ticlopidine is similar, but ticlopidine has the most serious side effects: nausea and diarrhea in 20% of patients, hemorrhage in 5% and neutropenia in 1% of patients. Therefore, **ticlopidine** is usually used in patients who cannot tolerate aspirin (hypersensitivity, bronchial asthma, etc.), at a dose of 250 mg/12 hours, orally. Ticlopidine is now rarely used to prevent thrombosis in patients who have had a coronary stent implanted.

Clopidogrel and prasugrel also inhibit the binding of ADP to receptors on platelets, specifically the P2Y12 receptor type. Both of these drugs can be given in combination with aspirin in patients with acute coronary syndrome (consisting of unstable angina pectoris, myocardial infarction with and without ST-elevation), as they lead to a reduction in mortality, repeated myocardial infarctions and stroke in such patients. Both clopidogrel and prasugrel are administered only once a day, in an oral dose of 75 mg (clopidogrel) or 5-10 milligrams (prasugrel). The most serious side effect of these drugs is bleeding from the gastrointestinal tract or in the brain.

Clopidogrel is used less and less, because, unlike prasugrel, its activity depends on the amount of **active metabolite** formed in the liver. In a number of patients, the formation of the active metabolite is weaker for genetic reasons, so clopidogrel will not be effective in them. Also, many drugs can affect the metabolism of clopidogrel and thus reduce or enhance its effect, which we often cannot control.

Ticagrelor also interferes with the action of ADP on P2Y12 receptors, but it does not bind to the ADP binding site, but to some other part of the receptor, with a reversible bond. Ticagrelor, like clopidogrel and prasugrel, is used in patients with acute coronary syndrome, because it leads to a reduction in mortality, repeated heart attacks and strokes in such patients. The efficacy of ticagrelor is the same or slightly higher than that of clopidogrel, and the most significant side effect is bleeding. Ticagrelor is administered orally.

Dipyridamole is used as an adjunct to oral anticoagulants when they cannot control thrombotic processes in the body on their own (e.g., in patients with artificial valves, at a dose of 75 mg/8 hours, orally). It is also used in combination with acetylsalicylic acid in the secondary prevention of ischemic cerebral infarction. Side effects of dipyridamole are: confusion,

abdominal pain and headache. The monoclonal antibody **abciximab** binds to platelets and prevents their aggregation. It is used only in a single intravenous dose, exclusively for the prevention of coronary artery thrombosis after percutaneous transluminal angioplasty or stent implantation. **Tirofiban** (a small, non-peptide molecule) and **eptifibatide** (a cyclic peptide) are also administered intravenously, in the same indications as abciximab.

FIBRINOLYTICS

Small thrombi that form in the blood vessels of a healthy person are normally immediately broken down by plasmin, a blood plasma enzyme similar to trypsin, which breaks fibrin chains. Plasmin is usually found in an inactive form (plasminogen) and is activated under the influence of a special substance released from damaged tissues (the so-called tissue plasminogen activator). Plasmin found in plasma inactivates alpha2-antiplasmin, while plasmin found in the thrombus remains active and breaks down fibrin, i.e., thrombus.

An already formed thrombus can be "broken up" by the use of drugs that activate plasminogen and convert it into plasmin. **Streptokinase** (obtained from a streptococcus culture extract) was first used, primarily for the treatment of recent myocardial infarction (within the first 12 hours), recent pulmonary embolism, and deep vein thrombosis. Streptokinase acts indirectly: it forms a complex with plasminogen, which activates it and converts other plasminogen molecules into plasmin. It is administered slowly intravenously, as an i.v. infusion. The dose of streptokinase for the treatment of myocardial infarction is 1,500,000 IU, administered in 100 ml of saline solution, which is infused slowly over 1 hour. The use of streptokinase is accompanied by the following complications in a small number of patients: bleeding, elevated body temperature, and allergic reactions. The elimination of streptokinase is biphasic: in the first phase (T1/2 = 12 minutes) the drug is distributed, and in the second (T1/2 = 25 minutes) the drug loses enzymatic activity. Streptokinase is now rarely used, because the risk of allergic reactions after its administration, especially repeated, is higher than with other thrombolytics.

Anistreplase is a complex of streptokinase and plasminogen that has been inactivated by the addition of an anisoyl radical. When injected intravenously, the anisoyl radical spontaneously lyses and streptokinase activates plasminogen. Since it is inactive at the time of administration, anistreplase can also be given as an i.v. injection, relatively quickly.

Urokinase is also a fibrinolytic; it is a dipeptide protease that is normally produced in the cells of the renal tubules. In practice, it is rarely used for thrombolysis, because it activates both circulating plasmin and thrombus-bound plasmin. It is not immunogenic. The half-life of urokinase is about 20 minutes.

A newer fibrinolytic is ***alteplase,*** a human tissue plasminogen activator produced by recombinant techniques (genetic engineering - the gene carrying the information for a protein is introduced into E. coli, which then synthesizes that protein in large quantities). Unlike streptokinase and anistreplase, alteplase is not immunogenic, i.e., it does not cause allergic reactions. It is believed that alteplase selectively acts on plasminogen bound in the thrombus, so complications are rare. However, rethrombosis is more common with the use of alteplase, probably due to its short half-life (5-10 minutes).

Two new variants of human tissue plasminogen activator are also used in practice today, ***reteplase*** (it has only those parts of the molecule that are necessary for binding to fibrin and proteolytic action) and ***tenecteplase.*** Reteplase acts faster and more effectively than alteplase (penetrates deeper into the thrombus), and tenecteplase binds more strongly to fibrin in the thrombus, has a longer duration of action than alteplase, and can be administered as an intravenous injection. Clinical studies of **desmoteplase**, which binds even more specifically to plasminogen bound in the thrombus, are underway**.**

After the completion of thrombolytic therapy, the patient should be given heparin and oral anticoagulants, as this reduces the frequency of re-thrombosis.

The main adverse effect of fibrinolytic therapy is bleeding (in the digestive tract or CNS). It can be prevented by inhibiting the conversion of plasminogen to plasmin with ***tranexamic acid*** or by direct inhibition of plasmin with ***aprotinin.***

Antifibrinolytics

Tranexamic acid and **aminocaproic acid** are sometimes used to suppress pathological fibrinolysis (locally or systemically) or lysis of the coagulum in subarachnoid hemorrhage, in order to prevent new bleeding. The dose of tranexamic acid is 15 mg/kg initially, then 30 mg/kg/6 hours orally or 10 mg/kg/6 hours intravenously. Side effects of tranexamic acid are epileptic seizures, visual disturbances due to retinal damage, intravascular thrombosis, and hypotension.

Aminocaproic acid can also be administered intravenously and orally. Serious side effects of aminocaproic acid are intravascular thrombosis, formation of a coagulum in the urinary tract with hematuria, and myopathy with muscle necrosis.

It is crucial for patient safety to distinguish between pathological fibrinolysis and disseminated intravascular coagulation (DIC), as the use of antifibrinolytics in DIC worsens the condition and leads to new intravascular thrombosis. In pathological fibrinolysis, the platelet count is more or less normal, while in DIC it is severely reduced; in DIC, the protamine paracoagulation test is positive, while in pathological fibrinolysis, the euglobulin clot lysis test is positive.

BLOOD AND BLOOD PRODUCTS OBTAINED BY BLOOD PROCESSING

Administering blood means administering a drug, but also transfusing liquid tissue. Therefore, administering blood is significantly more complicated than administering other drugs. First of all, the tolerance of the transfused blood must be ensured: it must be antigenically similar to the recipient's blood. The recipient and the blood donor must have the same blood group in the ABO and Rh systems, and the inter-reaction tests (recipient's serum with donor erythrocytes and donor serum with recipient erythrocytes) must be negative.

In principle, whole blood ("whole blood") is administered only when acutely lost blood needs to be replaced (e.g., in severe external or internal bleeding). In all other cases, individual blood elements should be administered separately. Whole blood is administered intravenously, in individual doses of 200 - 400 ml from one donor. When administering whole blood, an infusion system with a built-in filter must be used to avoid introducing large particles resulting from the aggregation and destruction of erythrocytes during blood clotting into the patient's bloodstream. Blood administration (transfusion) can only be performed by a doctor! After inserting a venous catheter and connecting a bottle of blood to it via the system, the doctor should administer about 50 ml of blood, and then stop the transfusion for the next 10 minutes. During this time, the patient is carefully observed, looking for signs of a transfusion reaction due to a possible incompatibility of the recipient's blood and the donor's blood (pain in the lumbar region, tachycardia, hypotension). Only if these signs are absent, further blood administration is continued, at a rate of about 10-20 ml/min.

Whole blood can be stored in a refrigerator at 4°C for up to 40 days after collection if it is previously stabilized with a preservative such as the CP2D-A mixture:

C - citrate (binds calcium ions and thus prevents coagulation)

P - phosphate

2D - double the amount of glucose compared to previous preservatives

A - adenine.

After blood transfusion, about 70% of erythrocytes survive for 24 hours. There are few platelets in whole blood, because they perish after 24 hours from the start of blood storage in the refrigerator. Also, whole blood contains only stable coagulation factors (2, 7, 9 and 11) as functional.

Instead of whole blood, only erythrocytes (so-called "**packed erythrocytes" or "erythromass**") can be used, which are obtained when plasma is separated from whole blood. Packed red blood cells are better used to replace lost blood (of course with physiological solutions) than whole blood because excess Na+, K+, lactic acid and citrate have been removed with the plasma. Red blood cells can be stored frozen ("frozen red blood cells"), but they cannot be used in emergencies.

A special preparation of erythrocytes is "**washed erythrocytes**". Here, the erythrocyte mass is washed in a physiological solution until the leukocytes and platelets are completely removed from the erythrocytes. This preparation of erythrocytes is used only in people who are allergic to some leukocyte and platelet antigens.

Platelet concentrates in a volume of 50 ml can also be made from blood. The shelf life of one concentrate is 5 days from the moment of blood collection. Platelet concentrates are used to treat thrombocytopenia.

Plasma can be separated from the blood and used to replace the volume of lost blood. Only if it is **fresh** (separated immediately after blood collection from the donor) or "**fresh frozen**" (frozen fresh plasma) does plasma contain unstable coagulation factors 5 and 8, so it can be used in addition to volume replacement and to treat coagulation disorders (e.g., hemophilia). For the treatment of coagulation disorders, specially prepared concentrates of individual coagulation factors or the so-called "**cryoprecipitate**" which is obtained from fresh plasma and contains all coagulation factors can be used. To compensate for the volume of lost blood as well as for the replacement of lost plasma proteins (e.g., in burns, nephrotic syndrome, etc.), **albumin concentrates** isolated from blood are used. These preparations are usually made in concentrations of 5% and 20%. When a total of 25g of albumin is administered, this represents the osmotic equivalent of 500 ml of plasma. The advantage of albumin over plasma is the inability to transmit hepatitis viruses.

A special procedure can be used to separate individual coagulation factors from the blood and concentrate them to a sufficient dose to treat conditions in which these factors are deficient. There are **factor 8 concentrates**, which are used to treat patients with hemophilia A, **factor 9 concentrates**, which are used to treat hemophilia B, and **activated factor 7 concentrates**, which are used

to treat patients with *von Willebrand disease*, as well as *coagulopathy after extreme bleeding* or during liver failure. In patients with hemophilia who have developed coagulation factor inhibitors (antibodies), a so-called anti-inhibitory coagulation complex is used, which contains already activated vitamin K-dependent coagulation factors.

Adverse effects of transfused blood and blood-derived products

Hemolytic reactions can occur after transfusion of whole blood or packed red blood cells if there is an ABO, Rh or other antigen group incompatibility between the donor and recipient. This can occur if there is a mistake in blood grouping or an interreaction. Hemolysis leads to hemoglobinemia and hemoglobinuria. Symptoms of hemolytic reactions include: a feeling of warmth and pain along the vein into which the blood is given, pain in the lumbar region (due to tubular necrosis and reactive inflammatory reaction), flushing, chest pain, fever, hypotension with tachycardia. Disseminated intravascular coagulation occurs in about 30% of patients**.**

Febrile reaction. An increase in body temperature can occur after the administration of whole blood, packed red blood cells, plasma, platelets or coagulation factors. This is a relatively common adverse reaction (about 1%).

Allergic reactions can also occur after the administration of blood, red blood cells, plasma, albumin or coagulation factors.

Infections. Syphilis, malaria, hepatitis B, C and E, AIDS, cytomegalovirus and a large number of bacteria that contaminate the collected blood can be transmitted through the administration of whole blood, red blood cells, platelets or plasma. Today, blood is routinely tested for syphilis, hepatitis B and C and AIDS in our country.

Thrombophlebitis at the site of transfusion and pulmonary edema are associated with prolonged transfusions and transfusions of excessively large amounts of these products.

COLLOID SOLUTIONS

Colloidal solutions contain particles of high molecular weight that have difficulty leaving the bloodstream through the pores in the capillary walls. Due to this, colloidal solutions raise the oncotic pressure of the plasma and attract water from the intercellular space into the blood plasma. The final effect is an increase in plasma volume (and therefore blood), so colloidal solutions are often called "plasma expanders". So far, the most widely used dextrans, gelatin and esterified starches have been.

Dextrans are polysaccharides that bacteria produce from glucose. **Dextran 70** contains particles weighing 70,000 daltons and is produced at a concentration of 6% in an isotonic glucose solution (5%). It is used for a short-term increase in plasma volume in acute hemorrhages. It interferes with blood group determination, so blood samples should be taken before dextran is administered. Care should be taken not to overdose (give a maximum of 500 ml to 1L in 24 hours) because it can lead to excessive expansion of plasma and intercellular space (some particles still escape from the capillaries), which is manifested by edema of the lungs and other tissues.

Dextran 40 contains particles weighing 40,000 daltons and is made in a concentration of 10% in an isotonic glucose solution. It is used primarily to improve blood flow through tissues when there is narrowing of the arteries of the extremities due to arteriosclerosis; the reason for this use is its property of reducing erythrocyte agglutination and blood viscosity. It has the same side effects as dextran 70.

Gelatin contains particles weighing about 30,000 daltons; it is made as a 4% solution in an isotonic sodium chloride solution (0.9%). It is used to replace lost blood volume. Like dextrans, gelatin can cause pulmonary edema and worsening of congestive heart failure.

Etherified starch is a starch composed of 90% amylopectin that has been etherified with hydroxyethyl groups. The molecular weight of the particles of etherified starch ranges from 200,000 to 450,000 daltons. It is made as a 6-10% solution in isotonic sodium chloride solution. It is used to replace lost blood volume. It can also cause pulmonary edema if overdosed (daily maximum up to 1.5L).

CRYSTALLOID SOLUTIONS

Crystalloid solutions are clear solutions of electrolytes or simple sugars in water. They are used as an intravenous infusion to replace the loss of water, electrolytes, or blood as a whole. The most commonly used solutions are isotonic with blood plasma (about 300 mOsmol/l): 5% glucose, 0.9% sodium chloride, complex physiological solutions (Ringer's solution [Ca2+ 2.2mM/l,

K+ 4mM/l, Na+ 147mM/l, Cl- 156mM/l], Hartmann's solution, i.e., Ringer-lactate [Ca2+ 2mM/l, K+ 5mM/l, Na+ 131mM/l, Cl- 111mM/l, HCO3-/in the form of lactate/ 29mM/l] and Darrow's solution [English: Darrow, Na+ 120mM/l, K+ 35mM/l, Cl- 105mM/l, lactate 50mM/l]) and combinations of NaCl with glucose. ("glucosaline" solution - 1:1 isotonic glucose and isotonic NaCl). Glucose solution is used when there is only a water deficit, while other solutions are used for the loss of both water and electrolytes. Derou solution is used when there is acidosis associated with hypokalemia.

To correct acidosis, a solution of NaHCO3 is used at a concentration of **8.4%** (then 1 ml of the solution contains 1 mM bicarbonate). This solution can be used as a slow intravenous injection or as an addition to the infusion of isotonic sodium chloride.

To correct hypokalemia, a **7.4% solution of KCl** is used (1 ml of this solution contains 1 mM potassium chloride). It is used as an addition to the infusion of isotonic sodium chloride, and is dosed according to the severity of hypokalemia (usually a dose of 30 mM every 8 hours is not exceeded).

PARENTERAL NUTRITION

Whenever a patient cannot take food orally for more than **7 days**, parenteral nutrition should be used. It is administered intravenously, via a central venous catheter, due to the high osmolarity of the solution (if administered via a peripheral vein, thrombophlebitis inevitably occurs).

An adult should be given **2000-2500 kCal per day with 10-14g of nitrogen from amino acids (1 g of nitrogen = 6.25 g of protein) in a total of 2-3 L** of fluid.

The solutions used should contain all essential and many non-essential l-amino acids. The energy sources that should be used in these solutions are glucose and fat emulsions. Glucose should provide **60%** of the energy, and fat about **30-40%** (**1 g of glucose = 4 kCal, 1 g of fat = 9 kCal**). Fat emulsions have the lowest osmolarity and can be administered via a peripheral vein, in addition to a central venous catheter. Fat emulsions, in addition to their energy value, have another: they contain essential fatty acids.

Parenteral nutrition solutions should also contain basic electrolytes (Na+, Cl-, K+, Ca2+), sufficient phosphate (20-30 mM per day) to ensure glucose phosphorylation, and macro- and microelements. Simultaneously with the start of parenteral nutrition, the patient should be given intramuscular loading doses of **vitamin B12 and folic acid**; other vitamins should be administered 2 times a week.

The patient's electrolyte status should be monitored frequently throughout the entire period of parenteral nutrition!

Adverse effects of parenteral nutrition are: **sludge formation** in the gallbladder, **cholestasis**, and disturbances in liver function test values. Febrile reactions may occur after the administration of fat emulsions; in addition, fat emulsions interfere with the measurement of partial pressures of oxygen and carbon dioxide and blood calcium concentration..

ENTERAL NUTRITION

In the literature, the term “enteral nutrition” was previously used loosely to refer only to certain methods of administering special food formulations to patients who are unable to take food in its usual form. Since 2006, when the European Society for Clinical Nutrition and Metabolism issued its guidelines for enteral nutrition, the term enteral nutrition has been precisely defined and includes “all forms of nutritional support that involve the use of a special diet for special medical purposes”. Enteral nutrition preparations are liquid, and are administered by the patient drinking them, or via a nasogastric or nasojeujunal tube. In the largest multicenter clinical study to date comparing enteral nutrition via nasogastric tube with nutrition via nasojeujunal tube, it was shown that there was no difference in clinical outcomes between the groups, including mortality, length of hospitalization, drug use, and incidence of aspiration pneumonia.

Enteral nutrition should provide approximately 25–30 kCal/kg/day. Enteral nutrition preparations can be divided into polymeric preparations, in which macromolecules of proteins, carbohydrates, and lipids dominate, digested preparations, in which macromolecules are mainly broken down to peptides, short-chain carbohydrates, and fatty acids, and preparations for special purposes, with a reduction in individual ingredients (e.g., a preparation with a reduced protein content, used in patients with renal failure).

VITAMINS

Vitamins were first defined by Hofmeister: "Vitamins are substances that are widespread in the animal and plant world, present in food only in small quantities, and are necessary for the growth and maintenance of the animal body." Vitamins are actually coenzymes, necessary for the functioning of most enzymes in human and animal cells. The old division of vitamins into fat-soluble (A, D, E and K) and water-soluble (B1, B2 complex / riboflavin, nicotinamide, nicotinic acid, folic acid, pantothenic acid /, B6, B12, C and H) is still valid. Vitamins D, K, B12 and folic acid are discussed elsewhere in the textbook.

Vitamin A (retinol). Vitamin A exists in nature in 2 forms: retinol (A1) and 3-dehydroretinol (A2). Vitamin A can also be synthesized in the human body from provitamin A - plant pigments alpha, beta and gamma-carotene. Vitamin A is abundant in animal liver, egg yolk and milk; carotenes are found in colored vegetables (carrots, green vegetables). There is a depot of vitamin A in the liver.

Vitamin A is oxidized in the body to its active forms: retinal aldehyde and retinoic acid. Aldehyde is a component of the visual purple, rhodopsin, and retinoic acid is a necessary factor for the growth of bones, teeth and epithelium.

Vitamin A deficiency (hypovitaminosis A) occurs in deficient nutrition. Symptoms include: night blindness, conjunctival keratinization, corneal clouding (Bitot's spots initially, later keratomalacia), defects in the development of the pineal gland and tooth enamel, keratinization of the skin, increased susceptibility to infections. The daily requirement for vitamin A is about 2000 IU.

Vitamin A is used for the prevention and treatment of hypovitaminosis. The therapeutic dose of vitamin A is 25000 IU / 24 hours, orally.

Side effects of vitamin A occur when there is an excessive accumulation of this substance in the body (hypervitaminosis A). Symptoms and signs of hypervitaminosis A are: dry and scaly skin, increased intracranial pressure, alopecia, swelling of the liver, spleen and long bones.

Vitamin A derivatives have also found therapeutic use. They can be divided into four generations according to the time when they came into widespread use. The first generation consists of **tretinoin and isotretinoin**. All-trans retinoic acid (tretinoin) is applied topically in the treatment of acne because it accelerates the desquamation of epithelial cells and thus prevents blockage of the sebaceous gland ducts. 13-cis-retinoic acid (isotretinoin) also has the same effect, but is used systemically to treat severe forms of cystic acne (0.5 mg/kg/12 hours, orally). The second generation of vitamin A derivatives includes **etretinate and acitretin**. Aromatization of the six-cycle in the retinoic acid molecule produces etretinate. Etretinate and acitretin have a beneficial effect on patients with psoriasis, especially if they have the pustular form. Acitretin is also used to treat discoid lupus due to its anti-inflammatory and antiproliferative effects. The side effects of isotretinoin and etretinate resemble hypervitaminosis A. In addition, they have a teratogenic effect. **Adapalene and bexarotene** constitute the third generation, while the fourth generation has only one representative: **trifarotene**. Adapalene is used as a topical preparation for the treatment of psoriasis, seborrhea, acne and ichthyosis. Adapalene side effects include skin redness, skin dryness, itching and chronic inflammation with hyperpigmentation. Bexarotene is indicated for the treatment of cutaneous manifestations of T-cell lymphoma, and is administered orally. Among the side effects, bexarotene causes leukopenia, hypothyroidism, hyperlipidemia and exfoliative dermatitis. The fourth generation representative, trifarotene, is used as a topical preparation for the treatment of acne. Side effects are the same as with third-generation adapalene: skin redness, skin dryness, itching, and chronic inflammation with hyperpigmentation.

Vitamin E (tocopherol). Vitamin E is found in the germs of various seeds, in green leafy vegetables and legumes (beans, peas). Vitamin E itself is easily oxidized and thus protects against the oxidation of other substances - primarily vitamin A and unsaturated fatty acids in cell membranes. It is believed that this antioxidant effect of vitamin E may be beneficial in many degenerative and malignant diseases, but this has not yet been proven in controlled clinical studies. The only confirmed consequence of vitamin E deficiency so far is hemolysis in premature infants.

The daily requirement for vitamin E is about 10 mg. Side effects of vitamin E have not been described.

Vitamin B1 (thiamine). Thiamine is a coenzyme in the reactions of oxidative decarboxylation of alpha-keto acids, especially pyruvate. It is found in animal liver, meat, black flour and legumes.

Vitamin B1 deficiency can lead to congestive heart failure (so-called wet beriberi) or to neuropathy, muscle atrophy, ophthalmoplegia, nystagmus, ataxia, and cognitive impairment ("dry beriberi"). Alcoholics can also develop vitamin B1 deficiency, manifested by Wernicke's encephalopathy. The daily requirement for vitamin B1 is about 1.5 mg.

Vitamin B1 is used to treat hypovitaminosis B1. Side effects are unknown. In neurological manifestations of thiamine deficiency and in severe deficiency in general, the vitamin should be replaced intravenously, in order to act as soon as possible and prevent the occurrence of irreversible damage to the nervous system. If a person has a thiamine deficiency, even marginally,

when receiving an infusion of glucose solution, it is necessary to give thiamine, otherwise acute heart failure will be provoked. Due to glucose metabolism, pyruvate and lactate accumulate, which cannot be further used in the Krebs cycle (pyruvate cannot be decarboxylated because there is no cofactor - thiamine).

Vitamins of the B2 complex. Riboflavin is a component of flavin-adenine-dinucleotide, a coenzyme that participates in the transfer of hydrogen in many reactions of cellular respiration and the metabolism of amino acids, fatty acids and carbohydrates. It is found in milk, liver, eggs and green leafy vegetables. The daily requirement for riboflavin is about 1.7 mg.

Riboflavin deficiency is manifested by inflammation of the lips (cheilitis), the appearance of cheilosis and eye disorders (photophobia, burning in the eyes, itching). Hypervitaminosis has not been described. Riboflavin is used only for the treatment of hypovitaminosis.

Nicotinamide is a component of the coenzymes nicotinamide-adenine-dinucleotide (NAD) and nicotinamide-adenine-dinucleotide-phosphate (NADP), which participate in hydrogen transfer reactions. Nicotinamide deficiency causes the disease **pellagra**, which is characterized by symptoms that begin with the three letters "D": Dementia, Dermatitis (brown skin color) and Diarrhea. The daily requirement for nicotinamide is about 20 mg. Nicotinamide is found in meat, liver, wheat bread and green vegetables. It is used only for the treatment of hypovitaminosis - pellagra.

Pantothenic acid is a component of coenzyme A (CoA) which is necessary for the metabolism of fatty acids and acetic acid. It is found in almost all foods (hence the name "pan"-tothenic acid; pan - everything, everywhere). The daily requirement for pantothenic acid is 10 mg. A deficiency of this acid leads to neuropathy manifested by paresthesias in the feet ("burning foot syndrome").

Vitamin B6 (pyridoxal) is a coenzyme in the reactions of transamination and decarboxylation of amino acids. It is found in meat, liver, black flour, green vegetables. The daily requirement for vitamin B6 is 2 mg.

Vitamin B6 deficiency causes irritability, convulsions, hypochromic anemia and peripheral neuritis. Seborrhea also occurs. The use of isoniazid leads to vitamin B6 deficiency, so it is used preventively together with isoniazid. On the other hand, an overdose of vitamin B6 can lead to sensory neuropathy.

In large doses (100-400 mg/day), vitamin B6 can alleviate idiopathic sideroblastic anemia.

Vitamin C (ascorbic acid) is an antioxidant that prevents the oxidation of enzymes necessary for the hydroxylation of proline. This allows the construction of high-quality collagen rich in hydroxyproline. Vitamin C also facilitates the conversion of folate to folinic acid, and is necessary for the normal metabolism of tyrosine and phenylalanine. The daily requirement for vitamin C is 60 mg. Vitamin C is abundant in lemons, oranges, tomatoes, rose hips, and cabbage. Vitamin C deficiency manifests itself in **scurvy** (damage to capillaries, bleeding, gingivitis, tooth loss) and impaired wound healing. Vitamin C should only be used to treat deficiency. Overdose of vitamin C leads to oxaluria, the formation of calcium oxalate kidney stones, and diarrhea.

Biotin (vitamin H) is a coenzyme for carboxylation. It is abundant in yeast and meat. The daily requirement is 0.25 mg. Vitamin H deficiency is manifested by dermatitis and alopecia. Deficiency occurs with excessive intake of raw eggs - the protein avidin from the egg white binds vitamin H and interferes with its absorption. Hypervitaminosis has not been described.

CALCIUM (Ca)

Calcium is one of the most abundant elements in the human body. It is essential as an intracellular secondary messenger that enables the smooth functioning of vital processes of excitation and contraction in nervous and muscular tissue. An increase in the concentration of calcium in the cytoplasm of presynaptic nerve endings is a necessary step that enables the release of neurotransmitters; for the secretion of both endocrine and exocrine glands, it is necessary that an increased concentration of calcium in the cytoplasm leads to the contraction of microtubules and the exocytosis of vesicles with secretion; in order for actin and myosin in muscle cells to interact and lead to contraction, it is necessary for calcium to remove the inhibitory effect of the troponin-tropomyosin complex.

Calcium in the extracellular space is an important regulator of the excitability of cell membranes of excitable tissues (nervous, muscular, glandular, cardiac and vascular). A decrease in its concentration in serum leads to hyperexcitability (arrhythmia, tetany), and an increase above normal values leads to depression of excitable tissues.

Calcium is necessary for the normal construction and growth of bone tissue. In addition, during bone resorption, the minerals released neutralize hydrogen ions; bone formation, on the contrary, leads to the release of these ions. Thus, bones are both a calcium depot and a reservoir of electrolytes and buffers.

Normally, about 30% of orally ingested calcium is absorbed in the small intestine. The main regulator of absorption is the steroid hormone 1,25 dihydroxy-cholecalciferol.

In the body of an adult human there is about **1200 g of calcium**. Over 99% of all calcium is deposited in the bones, mainly as hydroxyapatite. Due to the constant remodeling of the skeleton in adults, 250 mg to 1 g of calcium is released into the systemic circulation daily; during the day this amount is re-accumulated in the bones.

About 40% to 50% of the calcium in the serum is bound to plasma proteins, mainly albumin. A few percent of the serum calcium is bound to organic anions, and about 50% is in the free, ionized form. The free, ionized calcium is actually active, so the bound portion of serum calcium can be viewed as a calcium depot.

Calcium is mainly excreted in the feces, bile, and urine (99% of the filtered calcium is reabsorbed in the tubules).

It is useful to know that **1 mM calcium contains 40 mg of this ion** in order to calculate the required doses of calcium.

Calcium carbonate preparations are most commonly used for oral administration of calcium, while calcium gluconate and calcium chloride are used for parenteral (intravenous) administration. When dosing these preparations, it should be borne in mind that different calcium salts contain different amounts of calcium ions (due to different molecular weights), and that the dose should always be calculated according to the amount of calcium ions that the patient will receive.

Indications for the use of calcium preparations are: cardiac arrest (electromechanical dissociation), hyperkalemia, hypermagnesemia, hyperphosphatemia, hypocalcemia, osteoporosis prophylaxis, and verapamil intoxication. Calcium administration is contraindicated in the following situations: in patients receiving high doses of cardiotonics and in whom signs of toxicity are already visible on the ECG (because serious ventricular arrhythmias may occur), in existing cardiac arrhythmias (because they may worsen), in sarcoidosis (because hypercalcemia may occur), in hypercalcemia and hypercalciuria, in dehydration (because of hypercalcemia), and in situations where there is hyperparathyroidism or vitamin D poisoning (because of hypercalcemia).

Calcium preparations should be used with particular caution in patients with renal insufficiency, as they are prone to hypercalcemia. Calcium phosphate preparations should especially not be used, as hyperphosphatemia will occur in addition to hypercalcemia.

Adverse effects of calcium preparations

- All parenteral calcium preparations damage the wall of the vein through which they are administered; therefore, they should always be administered through a large vein.
- Too rapid intravenous administration of calcium preparations causes vasodilation with hypotension, nausea, cardiac arrhythmias or even cardiac arrest. Therefore, intravenous calcium injections should not be administered for less than 20 minutes!
- When hypercalcemia occurs due to calcium overdose, the following symptoms and signs occur: fatigue, weakness, abdominal pain, vomiting, constipation, polyuria, polydipsia, renal calculi, corneal calcification, depression, confusion, shortened Q-T interval and, ultimately, cardiac arrest. This syndrome, for ease of memory, can be expressed in popular language: "Bones, stones, cramps and groans!"
- Nephrolithiasis with prolonged use.
- Prolonged use of alkaline calcium salts (e.g. calcium carbonate) has been associated with the development of "milk-alkali" syndrome (hypercalcemia, alkalosis).

MAGNESIUM (Mg)

Magnesium is a divalent cation (Mg^{++}) that is mostly found intracellularly. As a cofactor of about 300 key enzymes, it participates in the regulation of a large number of key processes in the body, and above all, it stabilizes the cell membranes of excitable tissues (nervous and muscular). As a medicine, magnesium is used in the form of salts: magnesium sulfate, magnesium chloride, lactate, gluconate and carbonate.

Magnesium is a cofactor of enzymes that use adenosine triphosphate (ATP) as a source of energy. One of the most important such enzymes is the Na-K pump in the membranes of excitable cells, which ensures the establishment of the resting potential. If there is not enough magnesium, the excitability of nervous and muscular tissue increases because K^+ is not entered into the cells as needed. In addition to increased excitability, magnesium deficiency is also associated with increased urinary

potassium loss, so hypomagnesemia worsens hypokalemia. In clinical practice, it is known that **hypokalemia cannot be satisfactorily corrected unless magnesium deficiency is first corrected**.

Due to its stabilizing effect on the membranes of nerve and muscle cells (both smooth and striated), magnesium exerts anticonvulsant, antiarrhythmic and vasodilator effects, and in higher doses can lead to inhibition of neuromuscular transmission.

Magnesium oxide in contact with hydrochloric acid of the stomach acts as an antacid, increasing intragastric pH.

Magnesium sulfate, when taken orally, reaches the small intestine in high concentration, so that the intestinal contents suddenly become hyperosmolar. Under the action of osmosis, water from the intestinal wall moves into the lumen, distends the intestine and causes peristaltic contractions that end with defecation. The laxative effect of magnesium sulfate ("bitter salt") is based on this mechanism.

Magnesium can be administered orally or parenterally. The following magnesium salts are administered exclusively **orally**: magnesium gluconate, magnesium chloride, magnesium lactate and magnesium carbonate. Magnesium oxide is also administered orally. **Magnesium sulfate is administered both orally and parenterally** (intravenously or intramuscularly).

The average person has about 25 g of magnesium in their body. About 99% of this ion is located intracellularly, and the rest is distributed in the extracellular space. The concentration of total magnesium in serum ranges from 0.65 to 1.05 mM/l (if the concentration is expressed in milliequivalents, it is twice as high, because the magnesium ion has two valences). Of the total magnesium in serum, about 50% is in the free (ionized) state, which is actually physiologically active.

Magnesium is not metabolized, crosses the placenta and enters the milk. It is excreted primarily via the kidneys, and to a small extent via sweat and intestinal secretions.

Magnesium preparations are **indicated** in the following conditions: hypomagnesemia, arrhythmias caused by cardiotonic glycosides, ventricular tachycardia "torsades des pointes", treatment and prevention of new convulsions in eclampsia, constipation, bowel preparation for contrast X-rays, status asthmaticus, premature labor, cardiac arrest and prevention of arrhythmias after coronary bypass grafting.

Dosage

For the correct dosage, it is useful to know that **1 mM magnesium contains 24 mg of magnesium**. All doses given refer to an adult, unless otherwise stated. Different magnesium salts contain the following amount of elemental magnesium:

Table 25. Magnesium compounds

Magnesium salt	1 g contain elemental magnesium:	1 g contain elemental magnesium:
$MgCl_2$	120 mg	4.9 mM
Magnesium gluconate	54 mg	2.2 mM
Magnesium lactate	120 mg	4.9 mM
MgO	603 mg	24.8 mM
$MgSO_4$	99 mg	4.05 mM

Magnesium administration is contraindicated in: patients with AV block, as it may worsen the block, hypermagnesemia and dehydration.

Magnesium should be dosed carefully in renal failure, as hypermagnesemia may occur due to decreased excretion. When magnesium is administered parenterally during pregnancy for a period longer than 4 weeks, bone anomalies and congenital rickets may occur. Parenteral administration of magnesium immediately before delivery may lead to hypermagnesemia in the newborn, which is manifested by hypotension and depression of the central nervous system.

Magnesium is excreted in breast milk in concentrations twice those in serum, so breastfeeding is not recommended after administration of large doses of magnesium to the mother.

Magnesium exhibits its **side effects** mainly when hypermagnesemia occurs. Then the following occur: nausea, vomiting, thirst, flushing with sweating, arrhythmias, drop in blood pressure, drowsiness, depression, confusion, loss of tendon reflexes, muscle weakness, coma and respiratory depression. At significantly high serum magnesium levels (>5 mM), AV block occurs, followed by cardiac arrest. If administered orally, magnesium can cause abdominal cramps followed by diarrhea. The dangerous effects of high magnesium concentrations on the heart can be counteracted by intravenous administration of calcium preparations.

POTASSIUM (K)

Potassium is active in its ionized form (K+). It is predominantly an intracellular ion. Its concentration in cells is about 150 mM/l, and in the extracellular fluid 3.5-5 mM/l. Potassium is found in sufficient quantities in almost all types of food, especially in fruits and vegetables. The potassium ion is "pumped" from the extracellular space into the cytoplasm of cells by active transport. Active potassium transport is assisted by glucose and insulin. Through its channels in the cell membrane, K+ constantly slowly leaves the cell and maintains the resting membrane potential. When the cell is stimulated (excited), sodium channels in the membrane open, sodium enters the cell and leads to membrane depolarization. When the sodium channels are then closed, the potassium channels open, which now massively leave the cell and lead to repolarization, i.e. a return to the resting potential.

Potassium from the intracellular space is exchanged with hydrogen ions from the extracellular space. Thus, when acidosis occurs, H+ enters the cells and K+ leaves them; when alkalosis occurs, H+ leaves the cells and K+ enters the cells. The reverse is also true: hypokalemia leads to the exit of potassium ions from the cells and the entry of hydrogen ions into the cells, i.e., to extracellular alkalosis; hyperkalemia leads to the entry of potassium ions into the cells and the exit of hydrogen ions from the cells, i.e., to extracellular acidosis.

Finally, the secretion of hydrogen ions in the kidney is related to the intake of potassium. If potassium intake is insufficient, fewer hydrogen ions are secreted in the urine and mild acidosis occurs. On the other hand, acidosis leads to reduced potassium secretion, and alkalosis increases potassium secretion.

Potassium is well absorbed from the digestive tract. Its bioavailability is about 100%. It has already been said that the largest amounts of potassium ions are found inside the cells. Potassium is excreted primarily via the kidneys and very little via the sweat glands. Approximately as much potassium is excreted in 24 hours as is ingested with food. Potassium is excreted in the kidney primarily by tubular secretion, in the distal tubule and collecting ducts.

Indications for the use of potassium are hypokalemia and the cardiac toxic effects of cardiotonic glycosides.

A healthy adult consumes 40-80 mM potassium daily with food. Potassium should be administered only after its serum concentration has been determined and the deficiency has been established. Oral preparations should always be given during meals due to the irritant effect on the intestinal mucosa.

Potassium should only be administered intravenously diluted (maximum concentration 40 mM/l). Before starting the infusion, the bottle should be shaken well because potassium tends to settle in the lower parts of the bottle. The rate of intravenous potassium infusion should not exceed 10 mM/hour.

For the treatment of hypokalemia and the toxic effects of digitalis, a dose of potassium is administered that depends on the concentration of potassium in the patient's plasma. Usually, this is a dose of about 100 mM/day in adults and about 2 mM/kg/day in children, as an intravenous infusion. If potassium is administered orally, adults should be given 100 mM/day, and children about 2 mM/kg/day, divided into 3-4 doses.

Potassium should not be given to patients who have: hyperkalemia, Addison's disease, renal failure, dehydration, cardiac arrhythmias (as exacerbation is possible), severe burns (as all patients are prone to hyperkalemia) or hyperkalemic familial periodic paralysis.

Adverse effects of potassium preparations are:

- Ulceration of the esophageal, gastric or intestinal wall if the potassium preparation is retained for some reason (slow motility or obstruction) and breaks down, so that an extremely high potassium concentration is achieved that damages the mucosa. Ulceration may lead to bleeding or perforation.
- Hyperkalemia (arrhythmias, paresthesias, muscle weakness, confusion, hypotension, AV block, ultimately cardiac arrest).
- Intravenous administration of concentrated potassium solution is irritating to the vein wall and causes pain; this can be alleviated by the administration of lidocaine to the intravenous potassium solution (50 mg per entire potassium dose).

SODIUM BICARBONATE ($NaHCO_3$)

Sodium bicarbonate is an alkaline salt used to counteract acidosis. The normal concentration of bicarbonate in plasma is 24-30 mM/l.

Bicarbonates are normal components of plasma in which they perform a buffering role. When bicarbonates are taken orally, they neutralize acid in the stomach, and the excess bicarbonate is then completely absorbed in the intestines. If there is excess

bicarbonate in the blood, then it is excreted via the kidneys, alkalizing the urine. In the kidney, bicarbonate ions are filtered and then reabsorbed in the proximal tubule.

Indications for the use of bicarbonate are: metabolic acidosis, cardiac arrest, the need to alkalinize the urine as part of forced alkaline diuresis, and hyperkalemia.

For intravenous administration in adults, an 8.4% solution of sodium bicarbonate (1 mM/ml) is used, and in children a 4.2% solution (0.5 mM/ml). If sodium bicarbonate is given as an intravenous injection, the rate of administration in children should not exceed 10 mM/min. If given as an infusion, it can be diluted in saline or 5% glucose, and should not be administered faster than 1 mM/kg/hour.

RESPIRATORY TRACT PHARMACOLOGY

TREATMENT OF BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The word asthma is of Greek origin, and means "difficulty breathing". At the heart of bronchial asthma are inflammation and excessive reactivity of the bronchial tree, caused by an allergic reaction, cold air, physical exertion or infection. Under the influence of the aforementioned factors, a large number of biologically active substances are released from nerve fibers, mast cells, leukocytes and other cells. The released mediators cause swelling of the mucous membrane and spasm of the bronchial muscles, i.e., narrowing of the airways. If a connection between exposure to an allergen and the onset of an attack is established in a patient with asthma, we speak of "extrinsic asthma", and if the allergic etiology is not clear, we speak of "intrinsic asthma". A person with bronchial asthma has periods of improvement and deterioration. The goal of asthma treatment is to prevent attacks (prevention) and to stop attacks that have already occurred. About 5-6% of children and young people have asthma.

Chronic obstructive pulmonary disease (COPD) is a disease of the respiratory tract characterized by permanently reduced airflow and an exaggerated chronic inflammatory response to harmful particles and gases. Patients experience alternating exacerbations and remissions. COPD occurs in older people, usually long-term smokers, with a frequency of about 4%.

In the treatment and prevention of asthma attacks, we use two types of drugs: bronchodilators and anti-inflammatory drugs. Bronchodilators include beta2 receptor agonists, muscarinic receptor blockers, phosphodiesterase blockers, leukotriene receptor blockers and mast cell stabilizers. Corticosteroids are used as anti-inflammatory drugs.

Short-acting β2-receptor agonists, muscarinic receptor blockers, phosphodiesterase blockers, and corticosteroids (but administered systemically) are used to terminate asthma attacks; long-acting β2-receptor agonists, leukotriene receptor blockers, mast cell stabilizers, and inhaled corticosteroids are used to prevent attacks. Long-acting β2-receptor agonists, inhaled corticosteroids, phosphodiesterase blockers, and inhaled muscarinic receptor blockers are used to treat COPD.

Short-acting β2 receptor agonists can be selective and non-selective; selective (salbutamol, terbutaline, fenoterol, bitolterol) activate significantly more β2 receptors than β1 receptors, while non-selective (isoprenaline, orciprenaline, adrenaline) activate both β2 and β1 receptors equally. Adrenaline also activates α receptors.

Selective β2 receptor agonists are administered by inhalation or orally. The inhalation route of administration is preferred, and should be used whenever possible, because the side effects of the drugs are then far less pronounced.

METHOD OF ADMINISTRATION OF MEDICINES VIA INHALATION

If the patient who needs to use inhalation therapy is a person without reduced physical and intellectual abilities, he or she can be prescribed a medicine in a **metered dose inhaler**. With such an inhaler, a single press of the thumb releases a precisely determined dose of medicine into the air in the form of an aerosol or dry powder, which the patient should inhale using

the appropriate technique (the inhaler is closed with the lips, the patient simultaneously activates the inhaler with his or her thumb and inhales air, then holds the inhaled air for 10 seconds).

If the patient is unable to use a metered dose inhaler (children, the elderly, people with mental retardation), the medication is administered via a **nebulizer** (a dose of medication is introduced into the nebulizer, creating an aerosol that the patient inhales through a mask, without any special breathing technique) or a plastic chamber („spacer“) is placed on the metered dose inhaler from which the patient inhales the medication through a mask, without any special technique (after activating the metered dose inhaler, the medication enters the plastic chamber).

Adrenaline is administered subcutaneously. The effect reaches a maximum after 5-15 minutes and lasts up to 4 hours.

All short-acting agonists of the beta2 receptor have side effects due to the activation of beta1 and beta2 receptors in other tissues and organs: hand tremor, palpitations, increased blood pressure, arrhythmias, nervousness. These side effects are also present when using selective beta2 agonists, but to a lesser extent than with non-selective drugs. When using these drugs, special care should be taken in patients with coronary artery disease. Due to strong stimulation of the heart muscle and increased oxygen consumption in it, an attack of angina pectoris and even myocardial infarction may occur.

Of the phosphodiesterase blockers in the treatment of bronchial asthma, **theophylline** is the most widely used. As one of the methylxanthines, theophylline inhibits phosphodiesterase (an enzyme that breaks down cyclic adenosine monophosphate) and blocks adenosine receptors. Its effects in the body include relaxation of smooth muscles (hence bronchodilation), stimulation of the autonomic nervous system, and stimulation of the heart. In addition to causing bronchodilation, theophylline reduces respiratory muscle fatigue and has some anti-inflammatory effects. Theophylline is used to relieve asthma attacks, to treat exacerbations of chronic obstructive pulmonary syndrome, and to treat pulmonary edema. It is administered as a complex with ethylenediamine, which we call aminophylline.

There are large differences in the rate of metabolism of theophylline among asthmatics, so that the same doses of this drug lead to different concentrations in the blood. It is very useful to monitor the concentration of theophylline in the blood of patients receiving it, because the measured values can be used to precisely adjust the dose of the drug. Particular caution should be exercised in patients with heart failure, because in them the metabolism of theophylline is additionally slowed down.

Due to the effect of theophylline on the vomiting center, patients receiving it often complain of nausea and vomiting. Theophylline causes restlessness in patients, and in the case of the use of large doses, convulsions are possible. Theophylline has a stimulating effect on the heart, so arrhythmias can occur. Hypotension occurs due to vasodilation of blood vessels in the extremities. In order to avoid adverse effects on the heart and central nervous system, when aminophylline (theophylline) is administered intravenously, it should be administered as a slow intravenous injection, i.e., over 20 minutes.

Theophylline should not be used together with zileuton (a leukotriene synthesis inhibitor), as zileuton inhibits the metabolism of theophylline.

While theophylline is a non-selective phosphodiesterase inhibitor, a **selective phosphodiesterase type 4 inhibitor, roflumilast**, has recently been used to treat severe COPD. Roflumilast is not a bronchodilator, but works by reducing inflammation in the airways. It is administered orally and can be combined with other COPD medications, except theophylline. Its effect is primarily reflected in a reduction in the number of exacerbations per year. It is metabolized in the liver via cytochrome P450. It can cause depression and suicidal tendencies in predisposed patients, as well as weight loss.

Muscarinic receptor blockers reduce the effect of parasympathetic fibers on the bronchial tree, leading to bronchodilation and reduced mucus secretion. The muscarinic receptor blocker **ipratropium bromide** can be used to treat asthma attacks, but is less effective than beta2 agonists. Its proper place is in the treatment of COPD and chronic bronchitis accompanied by bronchospasm. As a quaternary ammonium compound, it does not pass through cell membranes, so it is used only by inhalation. It is practically not absorbed into the systemic circulation, so systemic antimuscarinic effects are absent or very weak (dry mouth). In addition to ipratropium, **tiotropium bromide**, a structural analogue of ipratropium, is also used by inhalation. Tiotropium causes longer-lasting bronchodilation than ipratropium, as it remains bound to M3 receptors for longer (up to 36 hours). Bronchodilation after administration of tiotropium lasts for 24 hours, which allows for once-daily administration. Tiotropium is used to prevent exacerbations of chronic obstructive pulmonary disease, while ipratropium is used to treat exacerbations. Similar to tiotropium are **aclidinium and glycopyrronium**, long-acting muscarinic receptor blockers that are inhaled for 12 and 24 hours, respectively.

The most common side effects of muscarinic blockers are dry mouth, nervousness, headache, nausea, and cough.

Drugs that affect the functioning of leukotrienes are used only to prevent asthma attacks, always together with at least one drug from other groups (e.g. long-acting beta-agonists and corticosteroids). **Montelukast** is a drug with an attractive mechanism of action: it blocks receptors for cysteinyl leukotrienes (C4, D4, E4), substances released by mast cells and thought to contribute to inflammation and bronchoconstriction in asthma. Montelukast is currently used only in the prevention of asthma, in

patients who respond poorly to conventional drugs. Its efficacy is not greater than that of beclomethasone. It is taken orally, in a single evening dose. Side effects include headache and abdominal pain. In addition to montelukast, **zafirlukast** is also used as a leukotriene receptor blocker. Both drugs are now also indicated for the treatment of asthma induced by physical exertion. It has recently been discovered that leukotriene receptor antagonists can also cause the undesirable Churg-Strauss syndrome, which consists of asthma, rhinitis, sinusitis, eosinophilia, and vasculitis.

Zileuton inhibits the enzyme 5-lipoxygenase, which converts arachidonic acid to leukotrienes; this reduces the synthesis of not only cysteinyl leukotrienes but also leukotriene B4.

Zileuton, montelukast, and zafirlukast are administered orally. Zileuton causes dyspepsia and, in a small number of patients, leads to an increase in serum transaminase levels. While zileuton increases the concentration of theophylline in serum (by inhibiting its metabolism), zafirlukast reduces the concentration of theophylline and increases the concentration of warfarin.

Asthma attacks can also be successfully prevented by the use of substances that prevent the release of inflammatory mediators. mediators from mast cells, leukocytes and other cells. These are **cromolyn (cromoglycate-Na) and nedocromil.** Cromolyn and nedocromil are used only by inhalation. Less than 1% of the substances used in this way are absorbed into the systemic circulation. Their side effects are rare and mild: nausea, mild stomach pain, mild joint pain, swelling of the parotid glands, dry cough.

Cromolyn and nedocromil quickly and effectively help with exercise-induced asthma, while in "external" asthma it takes several weeks for them to fully show their effect.

Corticosteroids are indispensable for both stopping and preventing attacks of bronchial asthma. They are always combined with some of the drugs from other groups. Corticosteroids are used by inhalation (beclomethasone, budesonide, fluticasone) for the prevention attacks, and systemic (methylprednisolone, prednisone) to stop attacks. Corticosteroids reduce inflammation of the airways and thus relieve asthma symptoms. They are very effective. If they are used systemically for a long time to prevent asthma attacks (several months), significant side effects occur: in children they can slow down growth and in adults they can cause osteoporosis; peptic ulcer may occur; cataracts may appear in the eye; iatrogenic Cushing's syndrome occurs.

Longer use of corticosteroids should be done by inhalation, because then side effects are less frequent and less serious; they are mainly reduced to candidiasis of the oral cavity and hoarseness. Rinsing the oral cavity and pharynx with water after each use of the aerosol can even prevent these side effects. Only if inhalation is not possible (e.g. mental retardation) should administer corticosteroids systemically (e.g. prednisone orally).

If asthma attacks cannot be successfully prevented by chronic use of inhaled corticosteroids, then additional improvement is achieved by the simultaneous use of long-acting beta2-agonists (salmeterol, formoterol, indacaterol). Combined preparations of corticosteroids and long-acting beta 2 receptor agonists are administered twice a day by inhalation. Their use is contraindicated during an asthma attack, because their effect begins slowly (after about an hour), and some constituents of the preparations can provoke paradoxical bronchoconstriction.

Salmeterol and formoterol administered by inhalation act for more than 12 hours, and **indacaterol and vilanterol** for as long as 24 hours, due to their liposolubility (they are retained in cell membranes). They can only be used in the prevention of bronchial asthma attacks, and in combination with corticosteroids. The use of long-acting β2-agonists alone is associated with worsening of the underlying disease: bronchodilation helps for a while, but as the inflammation of the bronchial tree progresses, the disease inevitably loses control with β2-agonists.

For severe forms of asthma that have an allergic etiology, i.e. they belong to the “extrinsic” asthma, biological drugs have been developed that neutralize certain mediators of inflammation and thus reduce airway swelling**. Benralizumab** binds to the interleukin 5 receptor (leading to apoptosis of eosinophils and basophils)**, mepolizumab and reslizumab** to interleukin 5 itself**, and dupilumab** to the interleukin 4 receptor. In addition to these four monoclonal antibodies, **omalizumab,** also a monoclonal antibody that binds to IgE antibodies, is also used. The last development in this area is **tezepelumab**, monoclonal antibody against timic stromal lymphopoietin, which is active in all types of asthma. Biological drugs are used as subcutaneous injections, once every h 15 to 30 days, as an additional therapy with inhalation. Biological drugs have been shown to be highly effective, as they significantly reduce the number of asthma attacks; at the same time, they are well tolerated – the most common side effects are allergic manifestations and an increased incidence of herpes or urinary tract infections. Reslizumab sometimes causes muscle pain and an increase in serum creatine kinase.

Finally, in the treatment of asthma, one should never forget that the patient should primarily take enough fluids, i.e., be well hydrated, in order to reduce the viscosity of bronchial secretions and facilitate their expectoration.

Table 26. Doses of drugs used in the treatment of bronchial asthma.

DRUG	ROUTE OD ADMINISTRATION	DOSE	DOSE INTERVAL	INDICATION
Salbutamol	inhalation	2 breaths	5 часова	Stopping asthma attack
Adrenaline	супкутано	0.3 mg	20 минута	Stopping asthma attack
Ipratropium bromide	inhalation	2 breaths	6 часова	Stopping asthma attack
Aminophylline	i.v.	250 mg	-	Stopping asthma attack
Cromolin	inhalation	1 breath	6 часова	Prevention
Methylprednisolone sodium succinate	i.v.	40 mg	-	Stopping asthma attack

EXPECTORANTS AND MUCOLITICS

When bronchitis is accompanied by significant secretions in the bronchial lumen, the elimination of this secretion by expectoration is essential for the prevention of bronchopneumonia. Bronchi that are blocked by secretions mean distal atelectasis of the lung tissue, i.e. increased susceptibility to infection.

In order to be easily coughed up, the secretions should be as thin as possible. Drugs that dilute bronchial secretions and facilitate their expectoration are called **expectorants**. The basic and most effective expectorant is plain water. Taking a sufficient amount of water orally is a prerequisite for diluting the secretions; in addition, inhaling water vapor allows water molecules to directly penetrate the secretions.

The active principles of herbal drugs from the **saponin group** have a strong expectorant effect. Partly by reflex action (irritation of the gastric mucosa reflexively increases the secretion of water and electrolytes in the bronchial mucosa), and partly by direct action on the secretion (they are surface-active substances), these substances facilitate expectoration. Saponin from the root of primrose (**Primulae radix**) is a very effective, available and inexpensive expectorant.

Potassium iodide (KJ) also has an expectorant effect (a single dose is 300 mg) when administered orally. Excessive use of iodide can lead to hypothyroidism, and potassium can cause ulcers in the proximal jejunum. It is not uncommon for patients to develop acne, a metallic taste in the mouth and swelling of the salivary glands. Due to significant toxicity, synthetic expectorants, such as **bromhexine**, are now more commonly used.

Bromhexine increases the amount of bronchial secretion, which becomes thinner and easier to cough up. After oral administration, its effect begins in half an hour to an hour, and the maximum increase in the amount of mucus can be expected after 2-3 days. Bromhexine is generally well tolerated; gastrointestinal complaints and increased levels of aminotransferases in the blood rarely occur. In addition to bromhexine, its active metabolite, **ambroxol**, is also used as an expectorant. The main side effect of ambroxol are gastrointestinal complaints. Mucolytics are substances rich in SH-groups. **Carboxycysteine and acetylcysteine** break disulfide bridges in the secretion and thus reduce its viscosity. Acetylcysteine, in addition to being a mucolytic, is also used to treat paracetamol poisoning. It binds to the toxic metabolite of paracetamol via its SH-group, thus neutralizing its effect on liver cells. Side effects of mucolytics include gastrointestinal tract irritation and exacerbation of cystitis. They should not be given to people with peptic ulcer disease because they can cause bleeding in the gastrointestinal tract. They are also contraindicated in children under 2 years of age.

Mucolytics, but also antitussives (cough suppressants), include the recombinant enzyme deoxyribonuclease 1 (**dornase alfa**), which is administered by inhalation using a nebulizer. This enzyme is used only in cystic fibrosis, where it thins thick secretions and makes them easier to cough up. As a side effect, it can cause pharyngitis and laryngitis with hoarseness.

Ivy extract is also useful in the treatment of bronchitis. The active principle of ivy (Latin name: **Hedera Helix**) is alpha-hederin, which is well absorbed and penetrates the tissues, where it prevents the downregulation of beta-2 receptors. Due to this effect, the number of beta receptors increases, which results in an enhanced effect of noradrenaline, i.e., bronchodilation and increased production of surfactant in type 2 pneumocytes. Nausea and vomiting often occur with the use of ivy preparations. The cause of this side effect is the saponin **hederacoside C**, which, as a surface-active substance, dissolves the protective layer of mucus above the gastric epithelium, exposing it to the irritating effect of hydrochloric acid. A similar side effect occurs with all preparations containing saponins, as well as with mucolytic drugs.

Table 27. Doses of expectorants and mucolytics.

DRUG	ROUTE OD ADMINISTRATION	DOSE	DOSE INTERVAL
Bromhexin	Oral	8 mg	8 h
Carboxycystein	Oral	375 mg	8 h
Acetylcystein	Oral	200 mg	8 h

PULMONARY SURFACTANTS

Pulmonary surfactants are drugs used in the treatment of respiratory distress syndrome in premature infants. The most commonly used are **beractant, calfactant** (bovine surfactants) and **poractant alfa** (porcine surfactant). Although several synthetic surfactants have been developed and have even received marketing authorization, they have all been withdrawn from use due to their lower efficacy than beractant, calfactant and poractant. Clinical trials with third-generation synthetic surfactants are currently underway, but the outcome is still uncertain. Surfactants are administered by "infusion" into the bronchial tree via an endotracheal tube. Once they reach the alveoli, they spread throughout them, reducing surface tension and preventing alveolar collapse. The most serious adverse effect is the occurrence of bleeding in the bronchial tree.

ANTITUSSIVES

Antitussives are drugs that suppress dry, unproductive cough. If the cough is accompanied by expectoration of secretions, the use of antitussives is contraindicated because it leads to secretion retention, bronchial obstruction, atelectasis and bronchopneumonia.

Antitussives can suppress cough by inhibiting the cough center in the brainstem (central antitussives) or by reducing the sensitivity of receptors in the cough-producing zones of the pharynx, larynx and trachea (peripheral antitussives). **Central antitussives** can be opioids or their derivatives (**codeine, morphine, dextromethorphan, pholcodine**), and can also act through other, non-opiate receptors (**butamirate, glaucine**). Opioid antitussives are more effective, but have a greater tendency to cause **respiratory depression**, sedation, constipation and addiction. Therefore, they are used to suppress the most severe forms of dry cough - in the case of infiltration of the cough zones by a malignant tumor. Of the opioid antitussives, the safest is **dextromethorphan**, which does not cause addiction at all, and the frequency of constipation is significantly lower. Non-opioid central antitussives are most often used today to suppress milder forms of dry cough. They are administered orally. Caution should be exercised when these drugs are administered to young children, because they are more likely to develop respiratory depression than adults. **Peripheral antitussives (prenoxydiazine, pentoxifylline)** do not have a tendency to cause respiratory depression, but are less effective in suppressing cough than central antitussives. A relatively effective and completely harmless antitussive is the extract (macerate) of marshmallow root (**Altheae radicis**). It contains mucous substances that coat the tussive zones and reduce receptor irritation. It is taken in small sips every 5-10 minutes.

It has also been shown that the use of simple syrup in children successfully suppresses dry cough. The mechanism of action is not clear, but it is certain that the preparation has no side effects.

Table 28. Doses of antitussives

DRUG	ROUTE OD ADMINISTRATION	DOSE	DOSE INTERVAL
Pholcodine	Oral	10 mg	8 h
Codeine	Oral	30 mg	8 h
Butamirat	Oral	50 mg	12 h

TREATMENT OF CROUP

Croup is a syndrome of upper airway obstruction accompanied by a characteristic cough that resembles a barking dog. Croup includes spasmodic (recurrent) croup, laryngotracheitis (viral croup), laryngotracheobronchitis, and laryngotracheobronchopneumonitis. When this syndrome occurs suddenly, most often at night, it is very important to calmly treat the child. If the child is hypoxic, give **heliox (a mixture of oxygen and helium**) or **oxygen** alone. The use of humidified air is no longer recommended, as it does not reduce the rate of hospitalization or the severity of the disease. Regardless of the severity of the croup, your child should be given **dexamethasone**, 0.6 mg/kg (maximum dose 10 milligrams) in a SINGLE dose orally, if possible, and if not, then intravenously or intramuscularly.

Another treatment option is **inhalation of budesonide** via a nebulizer. Corticosteroids take about 6 hours to work. The effectiveness of inhaled or systemically administered corticosteroids is very similar, but inhaled corticosteroids reduce the number of hospitalizations somewhat more. In addition to corticosteroids, in moderate to severe croup, **adrenaline** is also administered via nebulizer: 0.5 ml per kilogram (maximum dose: 5 ml) of adrenaline 1:1,000. The full effect of adrenaline occurs after 30 minutes and lasts about 2 hours.

OXYGEN

Oxygen is necessary for every cell to function in the respiratory chain, which enables the production of adenosine triphosphate (ATP), the main intracellular energy "coin". The lack of oxygen in the tissues is called hypoxia, and the reduced partial pressure of oxygen in the blood is called hypoxemia.

The indication for the therapeutic use of oxygen is hypoxemia (the partial pressure of oxygen is **less than 60 mmHg**, and the oxygen saturation of hemoglobin is **less than 88%**), which can occur due to a lung disease that makes gas exchange difficult (obstructive syndrome, pneumonia, pulmonary embolism, restrictive syndrome, etc.) or due to inadequate heart function (cardiogenic shock, chronic decompensated heart failure). The goal of oxygen therapy is to increase hemoglobin saturation above 90%.

In addition to the aforementioned indication, oxygen is also used as an antidote for carbon monoxide (CO) poisoning.

Oxygen is administered via mask or nasal cannula, usually at a concentration of **up to 28%.** Higher concentrations can only be used if the patient is not also in chronic hypercarbia (the partial pressure of carbon dioxide in the blood is permanently elevated). Hypercarbia often occurs in patients with chronic obstructive pulmonary disease. Such patients have a reduced sensitivity of the respiratory center to CO2, so they breathe only thanks to chemoreceptors in the carotid and aortic bodies that detect low levels of oxygen in the blood. If such a patient were to be given oxygen at a concentration greater than 28%, his chemoreceptors would stop sending impulses to the respiratory center and depression or complete cessation of breathing would occur.

The flow of oxygen delivered to the mask or nasal cannulas should not exceed **4 liters per minute**.

When it comes to carbon monoxide poisoning, oxygen can exceptionally be given at a concentration of 100%, even under increased pressure (hyperbaric oxygen), but for a short time (the half-life of carbon monoxide elimination when using 100% oxygen is about 90 minutes).

If oxygen is administered in higher doses than recommended for a long time, it exerts toxic effects on the lungs due to the formation of free radicals (N_2O_2, O_2^-, ON-) and damage to the endothelium of the pulmonary capillaries. Already 6-12 hours after breathing pure oxygen (100%), tracheobronchitis (dry cough, pain behind the sternum) and pulmonary edema occur, which often ends tragically because it does not respond to therapy. Therefore, it is extremely important to administer oxygen cautiously, in recommended doses (concentration up to 28%, flow up to 4 l/min).

PHARMACOLOGY OF GASTROINTESTINAL TRACT

EMETICS

The act of vomiting requires the coordination of multiple striated and smooth muscles, which is achieved by the vomiting center in the medulla oblongata. Vomiting occurs in several phases. The process begins with nausea, which is accompanied by sweating, mydriasis, pallor, and increased salivation. At the same time, the tone and peristalsis of the stomach decrease, and the tone of the small intestine increases. In the second phase, straining occurs, when an attempt is made to inhale while the larynx is closed. Due to the negative pressure created in the esophagus, the contents of the stomach begin to pass into the esophagus. Finally, the third phase occurs, when a strong, tonic contraction of the diaphragm and abdominal muscles pushes the stomach contents into the esophagus, and then out through the mouth.

The activity of the vomiting center is influenced by: 1) information from receptors in the stomach wall, 2) information from the chemoreceptor zone (located in the area postrema, on the floor of the 4th ventricle), and 3) information from the vestibular apparatus. Therefore, vomiting can be caused by irritation of the stomach, the presence of certain substances in the blood that activate receptors in the chemoreceptor zone (this zone does not have a blood-brain barrier), and excessive stimulation of the vestibular apparatus (for example, while riding a boat or bus). The following receptors are located in the chemoreceptor zone and the vomiting center, the stimulation of which causes vomiting: **dopamine D2 receptors, serotonin 5-HT3 receptors, opioid receptors, muscarinic, nicotinic, and histamine H1 receptors.** In the vestibular apparatus, activation of **muscarinic and histamine H1 receptors** leads to vomiting.

In case of poisoning, vomiting should be induced within 1 hour of ingestion. It is best induced with **syrup of ipecacuanha**, a South American plant (Cephaelis ipecacuanha) whose root and rhizome contain the alkaloid **emetine**. 15 ml of this syrup is given with about 200 ml of water, and this dose can be repeated after 20 minutes if vomiting does not occur. Inducing vomiting is contraindicated in: poisoning with acids and bases, poisoning with petroleum, poisoning with convulsive poisons and in the unconscious state of the patient (due to the possibility of aspiration of vomited contents into the respiratory tract).

Emetine induces vomiting by acting on the gastric mucosa, but also by directly acting on the chemoreceptor zone. However, it is also cardiotoxic, so if vomiting does not occur after the administration of syrup of ipecac, the doctor must perform gastric lavage (to prevent emetine from being absorbed). In the absence of syrup of ipecac, vomiting can be induced by ingesting a glass of water with a little soap or a large spoonful of table salt dissolved in it. Previously, vomiting was induced with copper or zinc salts, but today it is avoided due to the toxicity of these metals. Parenteral (subcutaneous) administration of apomorphine (2 mg) also effectively induces vomiting, but is avoided due to its depressant effect on the respiratory center. Apomorphine works better if the poisoned person drinks two glasses of water beforehand. If none of the above is available, vomiting can also be induced mechanically, by irritating the palate and pharynx with the tip of a thin leather strap or a finger (be careful of bites!).

ANTI-EMETICS

Antiemetics are drugs that prevent or stop vomiting. They block some of the receptors in the chemoreceptor zone, the vestibular apparatus, or the vomiting center itself.

Drugs that block muscarinic receptors (**scopolamine** is most commonly used) successfully prevent vomiting caused by stimulation of the vestibular apparatus. They are most effective if applied immediately before setting off on a journey. Scopolamine is usually applied in the form of a skin patch, because due to its high liposolubility it is well absorbed through the skin.

Histamine H1 receptor blockers (**promethazine, diphenhydramine, dimenhydrinate**) are effective in preventing vomiting caused by stimulation of the vestibular apparatus (during driving, or in Meniere's syndrome), but are also used to treat vomiting in the first trimester of pregnancy (hyperemesis gravidarum). The reason for this second use lies in long-standing experience: no teratogenic effects of antihistamines have been observed so far. There is not enough experience with other antiemetics when it comes to their use during pregnancy. However, it should be borne in mind that only severe forms of vomiting during pregnancy are treated with antihistamines. In most cases, the use of drugs is not necessary. **Dopamine D2 receptor blockers** have proven to be very effective antiemetics. Although classical neuroleptics (for example, prochlorperazine) have a strong antiemetic effect, due to their pronounced side effects (extrapyramidal syndrome, hypotension, cardiac conduction disorders, etc.), drugs with a slightly more selective effect are used. These are **metoclopramide and domperidone**. They are mainly used to treat vomiting in gastroenteritis, to treat vomiting after the use of cytostatics and to suppress vomiting during

childbirth and emergency surgical interventions. In addition to the effect on the chemoreceptor zone and the vomiting center, the aforementioned drugs accelerate gastric emptying (they increase the tone of the gastroesophageal junction, relax the pylorus, accelerate the peristalsis of the antral part), which significantly contributes to the overall antiemetic effect. The dose of metoclopramide is 10 mg/6 hours, orally or parenterally. Its side effects are drowsiness and extrapyramidal disorders. In addition, increased prolactin release and galactorrhea may occur in women. Domperidone does not penetrate the blood-brain barrier. A newer generation of antiemetics is made up of drugs that **block 5-HT3 receptors** (**ondansetron, tropisetron, granisetron**). They are extremely effective in preventing and treating acute vomiting after cytostatic administration. Since the beginning of their use, the tolerability of cytostatic therapy has increased significantly. Side effects of ondansetron are headache and a feeling of heat. **Palonosetron** is one of the newer drugs in this group that has the special property of successfully inhibiting both early and delayed vomiting after cytostatic administration, so it is preferred with highly emetogenic cytostatics (e.g. platinum derivatives). In severe forms of vomiting after cytostatic administration, patients are given corticosteroids, usually **dexamethasone**, in addition to the aforementioned therapy. Dexamethasone is also effective in preventing postoperative vomiting.

A major advance in the field of prophylaxis and treatment of postoperative vomiting and vomiting after the use of cytostatics is **aprepitant, a blocker of neurokinin NK1 receptors for substance P**. Aprepitant has a long-lasting effect after oral administration (like palonosetron) and successfully protects against vomiting for up to 48 hours. When used to prevent vomiting after the use of cytostatics, it is combined with dexamethasone and some of the 5-HT3 receptor blockers. On the other hand, it does not have a proarrhytmic effect, and there are no serious side effects other than hiccups. Recently, the use of alkaloids from Indian hemp (Cannabis sativa) has also begun, which have been shown to have a strong antiemetic effect (**tetrahydrocannabinol** and others). The effect has been observed incidentally in people who abuse drugs from the aforementioned plant (hashish and marijuana). The mechanism of action is not clear, but it has been found that they are very effective in cytostatic-induced vomiting. Synthetic tetrahydrocannabinol (drugs called dronabinol and nabilone) has been approved for the treatment of cytostatic-induced vomiting, but only as a second-line treatment, when other antiemetics have proven ineffective.

Tetrahydrocannabinol causes sedation (in about 30% of patients), ataxia, dry mouth and orthostatic hypotension.

Finally, **benzodiazepines** also have some antiemetic effect. However, they are only used in combination with other antiemetics, because they are not effective enough and because they cause severe sedation.

HYDROCHLORIC ACID AND DIGESTIVE TRACT ENZYMES

Hydrochloric acid (HCl) is used to treat hypo- and achlorhydria that accompany atrophy of the gastric mucosa. Lack of acid makes it difficult to digest food because pepsin is inactivated in a weakly acidic environment.

Hydrochloric acid is administered by pouring 1-4 ml of a 10% solution into 200 ml of water, and then drinking the diluted acid through a glass straw (to avoid damaging tooth enamel) during and after meals. Instead of a solution, solid substances that only release hydrochloric acid in the stomach can be used. Such a substance is **betaine hydrochloride**, 0.5 g of which releases an amount of HCl equivalent to the amount in 2 ml of the aforementioned 10% solution.

In exocrine pancreatic insufficiency (e.g. after chronic pancreatitis, after pancreatectomy, etc.), there is an insufficient amount of pancreatic enzymes in the lumen of the small intestine. As a result, proteins, complex carbohydrates and especially fats from food are not broken down but reach the distal small intestine and colon, causing bloating, cramps and loose stools. Patients with exocrine pancreatic insufficiency can be helped by the use of pancreatic enzyme preparations.

There are two types of these preparations:

1. **Ordinary pancreatin**, obtained by extraction from pig pancreas, which most often contains 200-600 IU of proteases (trypsin and chymotrypsin), 8000-20000 IU of lipase and 9000-22000 IU of amylase per capsule;
2. **Pancrealipase**, a preparation that has more lipase than other enzymes (330 IU protease, 5000 IU lipase and 2900 IU amylase per capsule).

Pancreatic enzyme preparations are given **during meals**. They are dosed individually, based on the improvement in the appearance and composition of the stool.

Side effects of enzymes are perianal irritation (in case of overdose), hyperuricemia and hyperuricosuria (due to increased absorption of purine bases, precursors of uric acid).

In practice, an extremely effective preparation of pancreatic enzymes (which is well tolerated by patients) has been shown to be a drug in the form of gastroresistant granules, under the trade name **Creon**. These specially made granules disintegrate only in the small intestine, which prevents stomach acid from denaturing and inactivating the enzymes.

ANTI ULCER THERAPY

Duodenal peptic ulcer is a consequence of hypersecretion of HCl in the stomach and the arrival of excessive amounts of this acid in the duodenal bulb. Gastric peptic ulcer is caused by reflux of bile from the duodenum and damage to the protective mucosal barrier, so that acid from the lumen of the stomach can penetrate into the submucosa and damage it. When it comes to treating duodenal ulcers, the goal is to reduce acid secretion; when it comes to treating gastric ulcers, the goal is to reduce acid secretion and increase the resistance of the mucosal barrier. In addition, the presence of **Helicobacter pylori**, a gram-negative bacillus, in the lumen of the stomach and duodenum favors the development of ulcers. If the presence of Helicobacter pylori is detected in a patient, the prevailing view today is that eradication therapy should be applied immediately.

HCl is secreted from the parietal cells of the gastric mucosa by the action of a potassium-hydrogen pump ("proton pump") that expels a hydrogen ion into the lumen (H+) and inserts a potassium ion (K+) into the cytoplasm. Since K+ passively returns to the lumen, it is accompanied by a chlorine ion (Cl-). Parietal cells contain H2 histamine receptors, the stimulation of which increases acid secretion. On the other hand, the release of histamine from mast cells of the gastric mucosa is regulated by acetylcholine and gastrin. Through their receptors, both substances increase the release of histamine, and thus acid secretion. **Histamine H2 receptor blockers (cimetidine, ranitidine, famotidine, nizatidine)** are very effective and can practically reduce acid secretion to a very small amount. They are used to treat duodenal and gastric ulcers, reflux esophagitis and Zollinger-Ellison syndrome (multiple ulcers due to a gastrin-secreting pancreatic tumor). These drugs (especially cimetidine) interfere with the synthesis of sex hormones (impotence, **galactorrhea, gynecomastia** may occur) and slow down the metabolism of many drugs in the liver microsomal system. They are administered both orally and parenterally. While the effect of cimetidine and ranitidine lasts about 6 hours, famotidine and nizatidine have a longer effect, 10-12 hours. The therapy lasts 6 weeks. If the ulcer does not heal after 6 weeks, the therapy should be repeated for the next 6 weeks in hospital conditions. If it is not possible to hospitalize the patient, drugs with a different mechanism of action should be tried. In the case of gastric ulcers, therapy can only be started after a biopsy of the ulcer has been performed by gastroscopy and cancer has been excluded by histological examination. Ulcers refractory to the use of H2 blockers alone often respond well if a selective M1 muscarinic receptor blocker - **pirenzepine** - is added to these drugs.

An unfavorable feature of H2 receptor blockers is the occurrence of **tolerance** after prolonged use.

HCl secretion can be completely eliminated by the use of **proton pump inhibitors**. **Omeprazole, pantoprazole and esomeprazole** are used to treat refractory ulcers that do not respond to the use of H2 receptor blockers and the Zollinger-Ellison syndrome. These drugs irreversibly inhibit the proton pump, so it is sufficient to administer only one daily dose. So far, no serious side effects of these drugs have been observed, but studies on mice have shown an increased incidence of gastrinomas in the antrum of the stomach. Also there are some data pointing to increased frequency of **pneumonia** in patients taking these drugs for long time. The most common mild side effect is headache (in 8% of patients); in addition to headache, diarrhea may occur. Since they are metabolized in the liver on cytochromes, proton pump blockers often interact with other drugs that patients are taking at the same time.

Recently, new drugs have appeared that inhibit the proton pump in a different way, by competing for the site on the proton pump to which the potassium ion binds. These are acid-stable substances, which, unlike proton pump inhibitors, act immediately. They quickly accept protons in the canaliculi of the parietal cells, because they are weak bases, and then inhibit the potassium binding site from the luminal side. Only one drug from this group is currently in use, **vonoprazan**. Vonoprazan is metabolized only by cytochrome 3C4, but has a lower potential for interactions with other drugs than proton pump inhibitors.

The acidity of gastric juice can also be reduced by using **antacids** that directly neutralize HCl. The best effects have been shown by antacids that act gradually and do not increase the pH of the gastric juice above 4, because then the **"rebound" phenomenon** does not occur, i.e. subsequent increase in HCl secretion (this phenomenon normally occurs if the pH is raised to 7 or higher). Such antacids are **aluminum hydroxide and phosphate, magnesium hydroxide, and aluminum-magnesium-trisilicate**. Today, antacids are rarely used alone in the treatment of hyperacidity, but usually as an adjunct to H2-blockers. In order for an antacid to heal an ulcer on its own, it must be administered in a large dose. About 140 mEq of an antacid should be taken 1 hour and 3 hours after each meal, and before going to bed. Antacids containing Mg++ tend to cause diarrhea, and antacids containing Al3+ tend to cause constipation and hypophosphatemia (because aluminum binds phosphates from the intestinal lumen and prevents their absorption). Antacids should be avoided in patients with impaired renal function because they may cause hypermagnesemia or aluminum accumulation. Antacids should not be administered concomitantly with other medications because they may interfere with their absorption.

In most patients with ulcers that are refractory to conventional therapy, Helicobacter pylori can be isolated from the antrum and duodenum. They should also be given an antibiotic to which this bacterium is sensitive. In addition to antibiotics, **bismuth subsalicylate** also has a beneficial effect on Helicobacter; therefore, it is often combined with antibiotics (do not forget to warn

patients that bismuth stains the stool black /except for colloidal bismuth preparations/). Helicobacter eradication is almost always accompanied by ulcer healing.

In order to safely eliminate Helicobacter pylori, it is necessary to simultaneously administer drugs that reduce acid secretion (some of the proton pump inhibitors) and antibiotics. Today, the first-line therapy is the so-called quadruple therapy, which lasts 14 days. The therapy is called "**quadruple**" because four drugs are used: **a proton pump inhibitor**, e.g. pantoprazole (40 mg, twice daily), **bismuth subcitrate or subsalicylate** (300 mg/6 hours), **tetracycline** (500 mg/6 hours) and **metronidazole** (500 mg/8 hours). The effect of this therapy is the eradication of Helicobacter pylori in 90% of patients. After these 14 days, the use of proton pump inhibitors (or H2 blockers) is continued only if the ulcer was complicated by bleeding or perforation.

In the event that the patient has not responded to the "quadruple therapy", so that H. pylori still exists, a two-week "triple therapy" is administered: **vonoprazan** (20 mg/12 hours) + **amoxicillin** (1g every 8 hours) + **clarithromycin** (500 mg/12 hours). This treatment leads to a cure in the vast majority of patients.

For the treatment of gastric ulcers, a preparation made of sucrose and aluminum (**sucralfate**) can be used as an additional agent, which coats the gastric mucosa and the ulcer floor, protecting them from hydrochloric acid. Sucralfate is not absorbed, but is eliminated in the feces, so there are no significant side effects. Sucralfate requires an acidic environment to become active, and is therefore never combined with other antiulcer drugs. There is a risk of bezoars in people with delayed gastric emptying. In addition to the treatment of gastric ulcers, sucralfate is used to prevent stress ulcers in intensive care patients and to treat rectal inflammation after radiation therapy for pelvic tumors (administered as an enema).

When administered orally, sucralfate causes constipation.

A special entity is acute, superficial ulcers that occur after the use of acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Due to the inhibition of prostaglandin E synthesis, normal blood flow in the mucosa is disrupted and necrosis of its surface layer occurs. These ulcers can now be successfully prevented by oral administration of **misoprostol** (a PgE1 derivative). Its side effects include intestinal colic, mild diarrhea, and uterine contractions (it is contraindicated in pregnancy).

Table 29. Doses of antiulcer drugs

DRUG	ROUTE OD ADMINISTRATION	DOSE	DOSE INTERVAL
Ranitidine	Oral	150 mg	12 h
	i.v.	50 mg	8 h
Mg-Al-trisilicate	Oral	500 mg	The tablet is dissolved in mouth between the meals and before bed
Omeprazole	Oral	20 mg	24 h
Sucralfat	Oral	1 g	1 g between the meals and before bed

PROKINETICS

Prokinetics are drugs that accelerate the propulsive motility of the gastrointestinal tract. They are used to treat paralytic ileus and intestinal paresis after abdominal surgery, as well as for the treatment of gastroesophageal reflux. Since the parasympathetic nervous system accelerates motility under physiological conditions, most prokinetics act through this system or mimic it. The first prokinetics in clinical use were acetylcholinesterase inhibitors, which reduce the breakdown of acetylcholine and thereby enhance and prolong its action. **Neostigmine** is administered parenterally, in a total dose of 2.5 mg, and shows moderate efficacy.

Prokinetics include **tegaserod and cisapride**, which act in two ways: they activate serotonin 5-HT4 receptors and release acetylcholine from nerve endings in the intestinal wall. **Prucalopride** is a prokinetic that acts only through selective activation of 5-HT4 receptors. Cisapride is somewhat more effective than neostigmine because, in addition to increasing motility, it also promotes fluid absorption from the intestinal lumen by some still unknown mechanism. The most common side effects are colic-like pain and tachycardia. The dose of cisapride is 10 mg/6 hours orally or 5 mg/6 hours intramuscularly. Cisapride has shown a tendency to prolong the QT interval in the ECG, which sometimes leads to serious ventricular arrhythmias. Therefore, its use is now limited to cases that do not respond to other prokinetics. Tegaserod is used only in irritable bowel syndrome with a predominant constipation symptom. It is well tolerated: its most common side effects are headache and diarrhea. Prucalopride accelerates gastric emptying and motility of the small intestine and colon; It is currently approved only for the treatment of chronic constipation, but it is also used for gastroparesis. Prucalopride does not have proarrhythmic effects, and its most common side effects are headache and abdominal pain due to excessive intestinal motility.

Metoclopramide also has a prokinetic effect, as it releases acetylcholine from cholinergic nerves and sensitizes gastric smooth muscle cells to acetylcholine. Metoclopramide is used to treat gastroparesis in diabetics, or after surgical interventions. It is also a useful adjunct to the treatment of reflux esophagitis.

Interestingly, the antibiotic erythromycin can also accelerate gastrointestinal peristalsis, as it activates receptors for the gastrointestinal hormone motilin. This effect is short-lived, as tachyphylaxis develops after a day or two.

The only drug that has been shown to prevent postoperative ileus is **alvimopan**. Several clinical studies have shown that alvimopan, when taken orally on the day of surgery and then postoperatively, can shorten the time to recovery of gastrointestinal function (i.e., flatulence and oral intake) by 10 to 28 hours. Alvimopan is a selective blocker of mi-opioid receptors located in the gastrointestinal tract, thereby eliminating the inhibitory effect of opioids on motility. It is approved only for short-term use of a few days, as a link has been observed with the occurrence of myocardial infarction with prolonged use.

SPASMOLITICS

Spasmolytics are drugs that reduce the tone of smooth muscles and thus stop spasms accompanied by colic-like pain. They are used to treat intestinal, biliary and renal colic. So far, the most effective spasmolytics are muscarinic receptor blockers that eliminate the effect of acetylcholine. These are: **scopolamine butylbromide, propantheline, oxyphencyclidine** and others. Propantheline is particularly suitable because, in addition to its antimuscarinic effect, it blocks nicotinic receptors in the parasympathetic ganglia of the digestive tract. Due to the quaternary nitrogen in its molecule, it does not penetrate the CNS and does not exhibit undesirable central effects. The dose of scopolamine butylbromide is 5 mg/8 hours intramuscularly. Calcium channel blockers, especially from the dihydropyridine group, also have an antispasmodic effect. Nifedipine has shown greater efficacy than muscarinic receptor blockers in clinical studies, so it should be given preference in the treatment of patients with colic.

There are also drugs that directly relax the muscles of the digestive tract. These are **mebeverine, alverine and peppermint oil**. They are used mostly for symptomatic therapy of irritable bowel syndrome and diverticular disease.

Alpha blockers **tamsulosin and silodosin** are used to facilitate the exit of calculi from the distal third of the ureter, because they relax the smooth muscles of that part. Alpha blockers are not used for biliary and intestinal colic.

The main side effects are headache and heartburn.

In any case, colic must be treated causally - by eliminating the cause of the spasm (for example, eliminating calculi from the ureter, removing obstruction in the digestive tract, etc.). Antispasmodics are only an auxiliary, symptomatic remedy, which should reduce the patient's suffering until causal therapy has an effect..

CONSTIPATION THERAPY

We can only talk about constipation when the elimination of feces is carried out less often than every other day. The most common causes are psychogenic (consciously or subconsciously suppressing the defecation reflex due to fear, shame, etc.) and improper diet (insufficient fluids, food with little residue). Constipation should therefore always be treated causally, by educating the patient about proper nutrition and proper habits. The drugs we use for constipation are called laxatives and can be classified into one of the following groups:

1) **Drugs that increase the volume of intestinal contents**. An increase in the volume of intestinal contents stretches the intestinal wall and causes defecation. The patient should first of all take enough fluids and food with a lot of indigestible residues (cellulose, pectin and lignin). These indigestible substances bind water to themselves, and thus increase the volume of the colon contents. There are a large number of cellulose preparations in the world, but in our conditions, the simplest and cheapest is to recommend that the patient take **wheat bran**, 2-3 full tablespoons a day, after soaking it in yogurt or milk for 30 minutes. It takes 4-5 days from the start of use to regulate the stool. This method of treating constipation is the best because it does not have any side effects.

2) **Osmotic laxatives**. Drugs from this group are not absorbed after oral administration, they remain in the intestinal lumen, increase the osmolarity of the contents and cause water to pass from the intestinal wall to the lumen. The amount of small intestinal contents increases, the intestinal wall stretches and peristalsis is established, which transports the contents into the colon. Now the colon wall stretches, a “mass” reflex is established and defecation occurs. The most commonly used osmotic laxatives today are

70% sorbitol, lactulose (a synthetic disaccharide that is not digested), **macrogol** (polyethylene glycol) and **bitter salt** (MgSO4). In our country, bitter salt is the most common (8-15 g is the dose, with plenty of water). Osmotic laxatives are not suitable for use in simple constipation because they cause cramps and emptying of almost the entire digestive tract. They are most often used to prepare the intestines for contrast X-ray studies (irrigography, cecography and others), for colonoscopy and to prevent the absorption of poisons after poisoning. Lactulose (a disaccharide made up of galactose and fructose) is broken down in the colon by bacteria. It produces a large amount of lactic acid, which lowers the pH of the colon and suppresses the growth of bacteria. In addition, the osmolarity of the contents increases, so water passes into the intestinal lumen and a defecation reflex is triggered. Lactulose is used for the treatment and prevention of hepatic coma in patients with severe cirrhosis and bleeding in the digestive tract (dose: 15 g/6 hours, orally).

3) **Laxatives that act as stimulants**. Drugs can stimulate neurons in the intestinal wall and thus accelerate propulsive motility. Anthraquinone derivatives are the active principles of many herbal drugs (**Folium Sennae, Cortex Frangulae, Aloe**) which, after oral intake and absorption, activate neurons in the colon wall. It takes about 8 hours after intake for the effect to be shown. Some synthetic substances, for example **bisacodyl and glycerol**, also act similarly. Bisacodyl is administered both orally and rectally, while glycerol is administered rectally only, in the form of an enema or suppository. The dose of bisacodyl is 10 mg orally or rectally, in the evening before bedtime.

Castor oil was once widely used as a laxative. In the small intestine, under the action of lipase, it releases **ricinoleic acid**, which has a stimulating effect on neurons in the walls of the small and large intestines. After just 2-3 hours of ingestion, the small and large intestines are emptied, accompanied by cramps and abdominal distension. Due to these side effects, castor oil is rarely used today.

Stimulant laxatives also include **prucalopride**, an agonist of 5-TH4 serotonin receptors, which was previously discussed in the chapter on prokinetics.

Stimulant laxatives should only be used occasionally and for a short period of time, as chronic use can damage neurons in the intestinal wall and worsen constipation.

4) **Stool softeners**. Sometimes it is necessary to make the stool soft and slippery to make the act of defecation as easy as possible. A painful anal fissure, a thrombosed external hemorrhoid, or a perineal abscess are such conditions. Stool softening can be achieved with **paraffin oil**. Chronic use of paraffin oil should be avoided because its droplets can still penetrate the intestinal wall and block the lymphatic channels. In addition, sometimes the patient has difficulty controlling his stool when using paraffin oil: small amounts of stool can slip through the anus and stain the laundry.

Instead of paraffin oil, detergents (surfactants) such as **dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, and docusate dioctyl sodium sulfosuccinate** can be used to soften the stool. These drugs reduce the surface tension of water and allow the soaking and softening of the colon contents. They work after 1-2 days, and are best administered rectally. If administered orally, they can be absorbed and have a toxic effect on the liver.

5) **Isoosmotic solutions for colonic lavage contain polyethylene glycol (macrogol)**, sodium sulfate, sodium chloride, sodium bicarbonate, and potassium chloride. The patient must drink 4 liters of such a solution in 2-4 hours. Liquid stools soon follow, which stop when all the liquid that has been drunk is expelled. The components of the liquid are not absorbed to a significant extent, so this is currently the most effective way to prepare the colon for surgery.

ANTIDIARRHOICS

Acute diarrhea, whether caused by bacteria or viruses, usually ends on its own, as the causative agents are eliminated with the stool. The most important therapy is to replace lost water and electrolytes. This can be done orally (if the patient does not vomit) or by intravenous infusions. A solution of sodium chloride and glucose is administered orally (due to the co-transport of Na+ and glucose in the epithelium of the small intestine), gradually, in small doses ("by the teaspoon"). The use of antibiotics does not affect the course of the disease, but only reduces the amount of excreted bacteria. Antibiotics should only be used for diarrhea caused by invasive bacteria that penetrate the intestinal wall and bloodstream (**salmonellosis, shigellosis, Campylobacter jejuni, Yersinia enterocolitica**). The antibiotic of choice for all these bacteria is **ciprofloxacin**, a drug from the quinolone group (twice daily 500 mg, orally).

Diarrhea caused by non-infectious causes (for example, radiation enteritis, irritable bowel syndrome, malabsorption and dyspeptic diarrhea) can be controlled by the use of **loperamide, eluxadoline or diphenoxylate**, drugs from the opioid group. These three substances have few central effects, and in the digestive tract they stimulate mi-receptors and inhibit propulsive motility. Eluxadoline also blocks delta opioid receptors, and significantly reduces secretion from the stomach, pancreas and liver, so it should not be used in people who have had their gallbladder removed or have had previous attacks of acute pancreatitis.

Diphenoxylate is often combined with atropine, which, with its antimuscarinic effect, further reduces propulsive motility. The use of these antidiarrheals is contraindicated if the infection is caused by invasive bacteria; The elimination of pathogens is reduced and their passage into the intestinal wall is facilitated. The dose of loperamide is 2 mg/6 hours orally. Side effects of loperamide and eluxadoline are abdominal pain, dry mouth, nausea and constipation. Diphenoxylate can cause nausea, itching, dizziness and numbness of the extremities. A specific type of diarrhea is diarrhea caused by ulcerative colitis or Crohn's disease (ileitis terminalis). These are autoimmune inflammatory diseases of the colon and small intestine. 5-aminosalicylic acid (5-ASA) has shown good effect, most likely preventing the synthesis of prostaglandins in the intestinal wall. 5-ASA can be administered as such (**mesalamine**), as a dimer consisting of two 5-ASA molecules linked by a covalent bond (**olsalazine**) or in a chemical bond with the sulfonamide sulfapyridine (**sulfasalazine**). All of these drugs are poorly absorbed, so 5-ASA reaches the colon and acts on the inflamed wall where the normal mucosal barrier has been destroyed. Side effects of 5-ASA and other drugs in this group are headache, abdominal pain, impaired absorption of folic acid (supplementary administration of folic acid is recommended), diarrhea and infertility in men. The dose of sulfasalazine is 1 g/8 hours orally.

Sulfapyridine from sulfasalazine is absorbed to a significant extent, and can cause side effects characteristic of all sulfonamides: hemolytic anemia and skin changes (Steven-Johnson syndrome).

The newest preparation of 5-ASA is **balsalazide**. When taken orally, it is not absorbed, reaches the colon, and there, under the action of bacteria, it is broken down into 5-aminosalicylic acid and inert 4-aminobenzoyl-beta-alanine.

When ulcerative colitis and Crohn's disease no longer respond to 5-ASA, it is possible to administer corticosteroids systemically or in the form of enemas. They can lead to remission of the disease but at the cost of serious side effects. The best effect of all corticosteroid preparations is achieved by **budesonide**, which is about 200 times more potent than cortisol, and after oral administration has low bioavailability (because it is very quickly metabolized in the liver to inactive products), so it acts predominantly on the gastrointestinal tract (systemic side effects are less pronounced). In the most severe forms of Crohn's disease, where there are multiple fistulas perianally and intra-abdominally, patients can be given the so-called "biological" therapy. These are actually drugs (usually of a protein nature) that are produced by living cells, most often grown in vitro, in so-called cultures. **Infliximab** is one of such drugs. It is a monoclonal antibody (chimeric mouse-human antibody) that neutralizes tumor necrosis factor alpha (TNFalpha), and thus reduces inflammation. Infliximab is administered as an intravenous infusion, once or a maximum of three times, with intervals of one month. The drug is very effective, and leads to the closure of fistulas.

When infliximab is administered, the patient develops fever, chills, chest pain, and hypotension. The aforementioned phenomena are transient, but the real danger lies in the immunosuppressive effect of the drug: resistance to infections is reduced and the risk of lymphoma increases.

In addition to infliximab, other biological drugs are also effective in the treatment of Crohn's disease: **natalizumab** (a humanized monoclonal antibody that binds to the alpha 4 subunit of human integrins, molecules found on the membranes of many types of leukocytes, and which are necessary for the leukocyte to attach to the vascular cell adhesion molecule [VCAM-1] and thus pass through the capillary wall into the colon tissue), **adalimumab** (a recombinant human monoclonal antibody that binds to tumor necrosis factor alpha [TNFalpha] and blocks its role in the inflammatory process) and **certolizumab** (a recombinant, humanized Fab fragment of the antibody against tumor necrosis factor alpha, which is conjugated to polyethylene glycol, which allows subcutaneous administration every 2 weeks). As with infliximab, after the use of these drugs, the human immune system is compromised, so there is a risk of developing serious infections and some malignant diseases.

For the treatment of more severe forms of ulcerative colitis, monoclonal antibodies are also used that block the action of tumor necrosis factor alpha (**infliximab, adalimumab, golimumab**), interleukins 12 and 23 (**ustekinumab**) or prevent the interaction between alpha-4-beta-7 integrin and mucosal addressin-binding molecule 1 (MAdCAM-1) in the intestines (**vedolizumab**). In patients who do not respond to monoclonal antibodies, Janus kinase inhibitors (these are enzymes that phosphorylate proteins, and represent the intracellular part of cytokine receptors) can be tried with **tofacitinib or upadacitinib**. Janus kinase inhibitors are administered orally. Finally, for severe forms of ulcerative colitis, a drug that modulates the sphingosine-1-phosphate (S1P) receptor, **ozanimod**, can be used. This drug, which can also be used to treat multiple sclerosis (as well as its similar fingolimod), prevents the release of lymphocytes from the lymph nodes.

A special form of diarrhea is the so-called post-antibiotic diarrhea. It occurs after prolonged use of broad-spectrum antibiotics, which disrupt the balance between bacteria in the colon. Milder forms of post-antibiotic diarrhea are treated by discontinuing further use of antibiotics and taking so-called **probiotics**, i.e. preparations containing non-pathogenic bacteria (lactic acid bacteria, bifidobacteria) mainly from beverages obtained by fermenting milk (yogurt, kefir, etc.). By colonizing the colon with non-pathogenic bacteria, the pathogenic bacteria that caused the diarrhea are suppressed. More severe forms of post-antibiotic diarrhea occur due to the overgrowth of the anaerobic bacterium **Clostridium difficile, whose exotoxins A and B** cause necrosis of the colonic epithelium and the development of pseudomembranous colitis. If toxins A or B are detected in the patient's stool, oral **metronidazole** should be administered immediately. If the patient is not cured in 7 days, oral **vancomycin** is also administered

for 14 days. In resistant cases, when vancomycin cannot cure the patient, a new oral antibiotic, **fidaxomicin**, is administered, which is also not absorbed, but is effective against Clostridium difficile.

MEDICATIONS FOR DISSOLVING BILIARY CALCULI

Biliary calculi are the result of increased cholesterol concentration in bile and decreased bile acid concentration. If calcium is not deposited in biliary calculi (i.e., if calculi are not visible on plain abdominal X-ray), they can be gradually dissolved by administration of bile acids. Orally administered, **chenodeoxycholic acid or ursodeoxycholic acid** are absorbed in the ileum, reach the liver via the blood, where they inhibit hydroxymethyl glutaryl-CoA reductase, a key enzyme involved in cholesterol synthesis. This reduces the cholesterol concentration in bile, and the concentration of bile acids increases, which gradually dissolve cholesterol from the calculi. Side effects of this therapy include bloating, diarrhea, and liver damage. Ursodeoxycholic acid is significantly less toxic to the liver, so it should be given preference in therapy, although it is more expensive. Bile acids should be taken for 1-2 years (with occasional breaks) in order for a calculus with a diameter of 1 cm to completely dissolve. Calculi larger than 1.5 cm in diameter should not be treated in this way because it takes too long for them to completely dissolve.

The dose of chenodeoxycholic acid is 250 mg in the morning and 500 mg in the evening, orally.

In addition to dissolving biliary calculi, ursodeoxycholic acid is also used to treat **primary biliary cirrhosis**. In this disease, ursodeoxycholic acid protects hepatocytes from the toxic effects of hydrophobic bile acids, thus delaying the development of severe forms of cirrhosis.

DIMETHICON AND ALGINATES

Dimethicone (simethicone) is a drug that prevents the appearance of foam in the digestive tract and thus reduces the amount of gas in the intestines, i.e. flatulence. It is used mostly in infants, to relieve cramps.

Alginates are substances that create a protective layer on the surface of the mucous membrane of the stomach and esophagus, so that the corrosive effect of gastric acid is disabled. Alginates are often combined with antacids. They are used to treat mild forms of gastroesophageal reflux. Both dimethicone and alginates are well tolerated.

ANTIMICROBIAL THERAPY

ANTIBIOTICS

Antibiotics are chemical compounds produced by living organisms that can, in low concentrations, stop the life processes of microorganisms (bacteria, rickettsia, chlamydia, fungi, protozoa, and viruses). They are divided into bacteriostatic (antibiotics that inhibit the growth of bacteria, but do not destroy them) and bactericidal (antibiotics that kill bacteria).

Table 30. Bactericidal and bacteriostatic antibiotics

BACTERICIDAL ANTIBIOTICS	BACTERIOSTATIC ANTIBIOTICS
Penicillins	Tetracyclines
Cephalosporins	Erythromycin (low concentrations)
Imipenem	Spectinomycin
Aminoglycosides	Lincomycin
Erythromycin (high concentrations) Cotrimoxazole (trimetoprim + sulphametoxazole)	Clindamycin
Vancomycin	Sulphonamides
Quinolones	Chloramphenicol

When applying antibiotics, there should be certain principles that are of great importance for a successful treatment outcome: (1) antibiotics should not be applied unless absolutely necessary; (2) Before starting the application of antibiotics, pus, exudate, or infected tissues should always be taken and sent to the microbiological laboratory; (3) The drug should be applied in sufficient dose; (4) The initiated antibiotic therapy should not be changed in the first 2 days, because the effects of treatment cannot be seen before 48h elepse after initiation of the treatment; (5) The administration of antibiotics should follow the drainage of pus collections, excisions of devitalized tissues and removal of foreign bodies; (6) When clinical improvement occurs, therapy should continue at least for three days to prevent recurrence; (7) Contra-indicated is the simultaneous application of bactericidal and bacteriostatic antibiotic, because bactericidal antibiotics act only on the bacteria that are multiplying, and bacteriostatics are precisely preventing the division of bacteria.

ADMINISTRATION OF ANTIBIOTIC COMBINATIONS

Whenever possible, in the treatment of patients with infections, we apply only one antibiotic, whose spectrum of action is narrow. This avoids disturbing the balance between bacteria in the colon and creating resistant strains, which can cause new infection and endanger the life of the patient. The treatment of infections caused by resistant strains is difficult and with uncertain outcome, because the choice of antibiotics is then strongly narrowed. Unfortunately, we are often in a situation where it is necessary to apply an antibiotics with wide spectrum of action, and in combination.

There are several indications for the application of the combination of antibiotics. These are:

1. Treatment of mixed bacterial infections. In such cases, two or more antibiotics are applied with different antibacterial spectrum, so that the therapy covers all causes.

2. Reinforcement of antibacterial effect on a particular microorganism. This can be achieved by a combination of antibiotics that act synergistically. The combination of penicillin with streptomycin or gentamycin shows exceptional efficiency in the treatment of infections caused by Enterococcus Faecalis or Staphylococcus aureus. Also, penicillins with an extended spectrum of action (or Cephallosporins) and aminoglycosides act synergistic against Pseudomonas aeruginosa. The effect of combination of sulphonamide and trimethoprim (Cotrimoxazole, Bactrim) is greater than the simple sum of effects of these two drugs. Amphotericin B and Flucitosine synergistically act on fungal infections.

3. Prevention of the occurrence of resistance in a microorganism. Probability of occurrence of resistance to two antibiotics in the same-time is incomparably smaller than the probability of resistance to each of them separately.

4. Treatment of heavy infections in which the microorganism was not isolated. The combination of antibiotics provides a wide anti-bacterial "cover" that guarantees a favorable effect on the causative agent.

The combinations of antibiotics also have their pitfalls. The risk of toxic effects increases, costs of treatment is higher, and antagonism between the antibiotics may appear if one is bacteriostatic and the other bactericidal. The classic example of antagonism is the treatment of a pneumococcal meningitis by combining penicillin and tetracycline. Such therapy is significantly less successful than giving only penicillin.

PROPHYLACTIC USE OF ANTIBIOTICS

Antibiotics can be used both to treat existing infections and to prevent them. The prophylactic use of antibiotics has long been questionable, but recent clinical trials have proven its validity in precisely defined indications. The basic idea behind prophylactic antibiotic use is to achieve a bactericidal concentration of antibiotics in the patient's blood at the time when bacterial invasion of the tissues is expected. Exposed to such a high concentration of antibiotics, the relatively small number of bacteria that have invaded the tissues will not be able to survive there.

The most important indications for prophylactic antibiotic use are:

1. **Preoperative use**

a. Antibiotics should not be used prophylactically for all surgical procedures, but only in specific situations. These include: all operations in which foreign material is implanted (vascular grafts, prostheses, etc.), operations on purulent processes, operations on the large intestine, trauma with extensive tissue devitalization, burns and long-term surgical interventions.

b. The antibiotic should be administered one hour before the start of the operation, and then its therapeutic concentration in the blood should be maintained during the operation and during the first 24 hours. The parenteral route of administration is practically the only one that comes into consideration.

c. One example of prophylactic use of antibiotics is preparation for operations on the head and neck with opening of the oral cavity, pharynx, esophagus or trachea (operations in maxillofacial and ear-nose-throat surgery). In patients undergoing such an intervention, clindamycin 600 mg i.v. should be administered. 30 minutes before the start of anesthesia, and then another 300 mg i.v. after 12 hours from the start of anesthesia.

2. Administration before percutaneous interventions on blood vessels, regardless of localization, especially if foreign material is implanted (stents, coils, etc.). The principle of prophylactic administration in this indication is the same as in the preoperative administration of antibiotics: the drug is administered intravenously, half an hour to an hour before the intervention, in only one dose.

3. Long-term use of a depot preparation of benzylpenicillin (benzathine-benzylpenicillin) in children who have had an attack of rheumatic fever in order to prevent the recurrence of attacks due to colonization of the pharynx with streptococcus.

4. Use of penicillin or erythromycin before tooth extraction or scaling in people who have had rheumatic endocarditis (to prevent bacteria from the mouth from settling on previously damaged valves).

5. Long-term use of depot benzylpenicillin (benzathine-benzylpenicillin) in children who have had their spleen removed due to traumatic rupture (because they are at high risk of pneumococcal infections).

6. Prophylactic use of isoniazid in unvaccinated people living in a household with a tuberculosis patient.

7. Prophylactic use of rifampicin in all members of a closed collective (e.g., a company of soldiers) if one of them develops meningococcal meningitis.

8. Use of low doses of antibiotics in patients with recurrent urinary tract infections in the previous period.

In addition to these indications, prophylactic use of antibiotics is also justified in patients with malnutrition, immune system defects, or in patients undergoing steroid, chemo- or radiotherapy therapy, if severe neutropenia develops.

The following table shows the most rational choice of antibiotics for the prophylaxis of infection in certain surgical interventions:

TYPE OF SURGERY	PROPHYLAXIS
Cardiovascular surgery: Abdominal aortic reconstruction Leg surgery involving a femoral incision Any vascular surgery involving the implantation of a graft or other foreign body Amputation of a lower limb due to ischemia Heart surgery Implantation of permanent pacemakers	Cefazolin 1g i.v. as a single dose or 1g/8 hours for 1-2 days OR cefuroxime 1.5g i.v. as a single dose or 1.5g/12 hours, total of 4 doses OR vancomycin 1g i.v. as a single dose
Gastroduodenal surgery	

Biliary surgery, including laparoscopic cholecystectomy in high-risk patients	Cefazolin 1 g i.v. as a single dose or 1 g/12 hours for 2-3 days OR cefuroxime 1.5 g i.v. as a single dose or 1.5 g/12 hours, total of 4 doses
Colon surgery, including appendectomy **Elective surgery**	The day before surgery, the patient should drink 4 liters of polyethylene glycol solution over 2 hours. On that day, he takes only liquids. At 1:00 p.m., 2:00 p.m., and 10:00 p.m. on the same day, the patient takes 1 g of neomycin and erythromycin orally.
Colon surgery, including appendectomy **Emergency surgery**	Cefazolin 2 g i.v. + metronidazole 500 mg i.v. as a single dose
Rupture of an abdominal hollow organ	Clindamycin 600 mg/6 hours i.v. + gentamicin 1.5 mg/kg/8 hours i.v. for 5 days
Head and neck surgeries that involve opening the mucosa of the oral cavity or pharynx	Cefazolin 2g i.v. as a single dose OR clindamycin 600-900 mg i.v. as a single dose + gentamicin 1.5 mg/kg i.v. as a single dose
Neurosurgical operations, clean, without implants	Cefazolin 1 g i.v. as a single dose OR vancomycin 1 g i.v. as a single dose
Neurosurgical operations, clean - contaminated (through sinuses or nasopharynx)	Clindamycin 900 mg i.v. as a single dose OR Cefuroxime 1.5 g i.v. + metronidazole 0.5 g i.v.
Neurosurgical operations, cerebrospinal fluid shunt implantation	Vancomycin 10 mg into the cerebral ventricles + gentamicin 3 mg into the cerebral ventricles
Hysterectomy, vaginal or abdominal	Cefazolin 2 g i.v. as a single dose 30 minutes before surgery OR cefuroxime 1.5 g i.v. 30 minutes before surgery
Cesarean section during active labor or for premature rupture of membranes	Cefazolin 1 g i.v. as a single dose as soon as the umbilical cord is clamped
Abortion in the second trimester	Cefazolin 1 g i.v. as a single dose
Hip replacement, spinal fusion	Cefazolin 1 g IV as a single dose or 1 g/8 hours for 1-2 days OR Cefuroxime 1.5 g IV as a single dose or another 750 mg/8 hours, total of 3 doses OR Vancomycin 1 g IV as a single dose
Implantation of other joint prostheses	Cefazolin 2 g IV as a single dose OR Cefuroxime 1.5 g IV as a single dose or another 750 mg/8 hours, total of 3 doses OR Vancomycin 1 g IV as a single dose
Open reduction of a closed fracture with internal fixation	Ceftriaxone 2 g i.v. or i.m. as a single dose
Placing a peritoneal dialysis catheter	Vancomycin 1 g as a single dose 12 hours before surgery
Urological surgeries - prophylaxis is used only if the patient has bacteriuria	Cefazolin 1 g i.v. every 8 hours, 3 doses, followed by bactrim orally for 10 days
Transrectal biopsy of the prostatic gland	Ciprofloxacin 500 mg orally 12 hours before biopsy and 500 mg orally 12 hours after biopsy
Breast surgery	Cefazolin 1 g i.v. as a single dose
Traumatic wound	Cefazolin 1 g/8 hours i.v. for 5 days

CHOICE OF ANTIBIOTICS

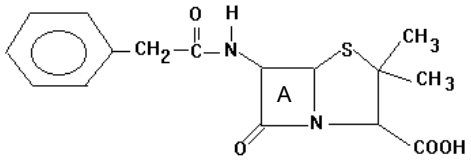
Whenever a patient's condition requires the use of antibiotics without delay, we choose the drug based on our clinical experience, knowing the most common causes of infections in certain locations in the body, and bearing in mind the level of resistance of bacteria in the environment in which we work. Antibiotic therapy determined in this way is called **empirical** antibiotic therapy. However, antibiotic treatment should not be started without first taking samples of infected tissues, examining them under a microscope, and inoculating them on nutrient media. This does not require much time, and is of enormous importance for the continuation of therapy, especially if after a few days it turns out that the antibiotic used was not effective. When the results of the sensitivity of bacteria isolated from our patient's tissues arrive (known in jargon as an "antibiogram"), we can then choose the antibiotic to which the isolated bacteria are sensitive. The antibiotic therapy chosen in this way is called **"targeted"** therapy.

Advances in medical technology have made it possible to identify a specific pathogen within a few hours by demonstrating the presence of small amounts of pathogen-specific DNA in infected tissues. However, even when this is done, the finding must be confirmed by classical culture and isolation of microorganisms on nutrient media.

BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics include penicillins, cephalosporins, monobactams, and carbipenems. All of them contain a beta-lactam ring in their molecule and act bactericidally by preventing the synthesis of the bacterial cell wall. The beta-lactam ring has 4 atoms and can be seen in the picture of the penicillin G molecule.

Penicillins. They are effective mainly against gram-positive bacteria. At therapeutic concentrations, penicillins are bactericidal. The resistance of some bacteria to penicillins is based on the production of the enzyme beta-lactamase, which breaks down the beta-lactam ring.



PENICILIN G (BENZIL PENICILIN)
A = beta-laktamski prsten

Penicillins can be classified into four groups:

1. **Natural penicillins G (benzylpenicillin) and V (phenoxymethylpenicillin).** They are highly active against gram-positive and gram-negative cocci, but are easily degraded by beta-lactamase.
2. **Penicillinase-resistant penicillins** (nafcillin, oxacillin, cloxacillin, dicloxacillin). They have a lower potency than the first group, but they also act on resistant strains.
3. **Broad-spectrum penicillins** (ampicillin, amoxicillin, bacampicillin). They also act on gram-negative bacteria, but are inactivated by penicillinase.
4. **Extended-spectrum penicillins** (carbenicillin, ticarcillin, azlocillin, mezlocillin, piperacillin). They also act on Pseudomonas, Proteus, Enterobacter and Klebsiella.

Natural penicillin G (benzylpenicillin) can be found prepared in vials, and after dissolution it is administered as a continuous intravenous infusion due to rapid elimination. After dissolution, the penicillin G preparation is clear, which is why it is called "crystalline" penicillin in the jargon. In order to ensure the presence of sufficient concentrations of penicillin G in the blood without the drug being administered as an infusion, depot preparations of penicillin G have been made, in which it is bound to certain substances from which it is gradually released after intramuscular injection and enters the bloodstream. When 2 molecules of penicillin G are bound to one molecule of dibenzyl-ethylene-diamine, **benzathine-benzylpenicillin** is formed, which can be administered once every 1-3 weeks, and the blood constantly contains concentrations of penicillin G above the minimum inhibitory concentrations for sensitive bacteria. There is also a depot preparation of **penicillin G procaine**, where one molecule of penicillin G is bound to one molecule of procaine; this preparation is administered once a day as an intramuscular injection.

Penicillin G is active against the following types of bacteria: streptococci, pneumococci, staphylococci that do not produce beta-lactamase, gonococcus, meningococcus, clostridia, treponema, actinomycetes and bacteroides (except Bacteroides fragilis). It shows partial activity against Corynebacterium diphtheriae and Bacillus anthracis. The spectrum of action of penicillin V is similar to that of penicillin G, but the latter is 10 times more active against meningococcus and gonococcus. Penicillin V is administered orally, and penicillin G only parenterally.

Cloxacillin and dicloxacillin are suitable for the treatment of mild infections caused by beta-lactamase-producing staphylococci because they are administered orally. Oxacillin and nafcillin are used parenterally to treat more severe infections caused by the same bacteria.

Ampicillin and amoxicillin, as well as others in the same group, are active against Salmonella, Shigella, H. influenzae, some strains of E. coli, and Proteus. They also act on Streptococcus faecalis. These drugs are acid-resistant, so they can also be administered orally. When combined with the beta-lactamase inhibitor sulbactam, ampicillin also acts on the multidrug-resistant bacterium Acinetobacter, one of the most common causes of hospital-acquired infections.

Carbenicillin and ticarcillin also act on Proteus and Pseudomonas. The only difference is that ticarcillin is more potent. They are administered parenterally, often (especially ticarcillin) in combination with the beta-lactamase inhibitor clavulanic acid. Azlocillin is even more active than ticarcillin when it comes to Pseudomonas.

Mezlocillin and piperacillin are more active than other penicillins against Pseudomonas and Klebsiella. Piperacillin is also combined with the beta-lactamase inhibitor tazobactam, which, along with its broad spectrum, reduces the possibility of pathogens being resistant to therapy. Today, piperacillin with tazobactam is one of the few drugs that are most effective in the treatment of Pseudomonas infections.

Table 31. Daily doses of penicillin preparations
(calculated for a healthy, young man weighing 70 kg).

DRUG	ORAL DOSE	PARENTERAL DOSE
Penicillin G	-	6- 20.000.000 IJ i.v.
Procain – PenicillinG	-	600.000 IJ/12 ha i.m.
Benzatin – penicillin G	-	1.200.000 IJ i.m.
Penicillin V	500 mg/6 h	-
Oxacillin	500 mg/6 h	1,5 g/6 h i.v., i.m.
Cloxacillin	250- 500 mg/6 h	-
Dicloxacillin	250 mg/6 h	-
Nafcillin	1 g/6 h	1 g/6 h i.v., i.m.
Ampicillin	500 mg – 1g/6 h	6- 12 g (divided in 4 doses) i.v., i.m.
Amoxicillin	250- 500 mg/8 h	-
Carbenicillin	-	5 g/6 h i.v., i.m.
Ticarcillin	-	200- 300 mg/kg i.v.
Azlocillin	-	4 g/6 h i.v.
Piperacillin	-	4 g/6 h i.v.

Side effects of penicillin. The most common side effect is allergy to penicillin. It can be any of the 4 types of allergic reactions, but the most common is the first type, anaphylactic reaction. Ampicillin causes a maculopapular rash in 5% of patients that does not represent an allergic reaction (especially if used in children with viral infections). Intrathecal administration of penicillin is contraindicated because in higher concentrations it causes convulsions (it acts as an antagonist of glycine and GABA). When using higher doses of penicillin G intravenously, hypernatremia or hyperkalemia is possible, depending on whether the drug is administered in the form of a sodium or potassium salt.

If anaphylactic shock occurs after the administration of penicillin, it should be treated first with adrenaline (0.5 mg i.m. or 0.2 mg i.v., diluted 1:10 with saline; the adrenaline injection can be repeated after 5 - 10 minutes if there is no improvement), then corticosteroids (e.g. methylprednisolone 80 mg) and antihistamines.

Penicillins are generally not metabolized in the body, and are excreted unchanged by the kidneys, via tubular secretion and filtration. Penicillins penetrate poorly through the intact blood-brain barrier, but their passage increases sufficiently during infections of the central nervous system that they can be used for their treatment.

Cephalosporins. According to the time of introduction into clinical practice, cephalosporins are divided into five generations. Generations differ from each other primarily in terms of their spectrum of action.

First generation cephalosporins. Antibiotics from this group are active against streptococcus groups A, B, C and G, S. viridans, pneumococcus, S. aureus and epidermidis, E. coli, Proteus mirabilis and Klebsiella. The most useful first generation cephalosporins in clinical practice are: cefazolin and cefadroxil for parenteral administration, and cephalexin and cephradine for oral administration. All of these drugs, except cefadroxil, have a short half-life, so they require administration at intervals of no longer than 6 hours. Cefazolin has shown excellent results in preoperative antibiotic prophylaxis. Other drugs from this group should never be used as drugs of choice because there is always a more effective or cheaper solution.

Second generation cephalosporins. These drugs have a broader spectrum than first-generation cephalosporins, so they also act on: Citrobacter, Enterobacter, a larger number of strains of E. coli, Klebsiella and Proteus mirabilis. Except for cefaclor, all other second-generation cephalosporins are administered only parenterally. Compared to the first generation, drugs from this group are characterized by greater resistance to beta-lactamases. The second-generation cephalosporins include: cefaclor, cefamandole, cefoxitin, cefuroxime, cefotetan, etc. Cefaclor is very useful for the treatment of otitis media, sinusitis, respiratory

infections caused by Haemophilus influenzae and urinary infections in pregnancy. Other drugs from the 2nd generation are used for the treatment of surgical infections in the abdomen and for preoperative prophylaxis.

Third-generation cephalosporins. Cephalosporins from this generation have an even broader spectrum of action against gram-negative microbes (they are very active against H. influenzae and against resistant strains of other gram-negative bacteria that are most often found in the hospital environment), but they are less effective against staphylococcus than drugs from previous generations. Except for cefpodoxime and cefixime, all of them are administered only parenterally. Given that they have little effect on anaerobic bacteria, if their presence is suspected, 3rd generation cephalosporins should be administered in combination with a drug effective against anaerobes (clindamycin, metronidazole). Most of these drugs penetrate the blood-brain barrier well, so they can be successfully used to treat infections of the central nervous system. This group includes: cefpodoxime, cefixime, cefotaxime, ceftriaxone, ceftazidime, cefoperazone and moxalactam. Cefotaxime and ceftriaxone are used successfully for the treatment of severe infections in the abdomen and pelvis, while ceftazidime is currently the drug of choice for infections with Pseudomonas aeruginosa.

The new cephalosporin that most closely matches the characteristics of the third-generation cephalosporins is **ceftolozane**, which is only available in combination with tazobactam, an extended-spectrum beta-lactamase inhibitor. The ceftolozane/tazobactam combination is particularly effective against Pseudomonas and other gram-negative enterobacteria (but not against carbapenem-resistant ones), and is also active against anaerobic bacteria and streptococci. It is used in the second-line treatment of nosocomial pneumonia, intra-abdominal and urinary tract infections, usually caused by multidrug-resistant gram-negative bacteria.

Another third-generation cephalosporin has recently been prepared in combination with a beta-lactamase inhibitor, in order to be effective against multidrug-resistant strains of Pseudomonas: **ceftazidime with avibactam**. The advantage of ceftazidime/avibactam over ceftolozane/tazobactam is reflected in the fact that the former is also active against carbapenem-resistant Pseudomonas. It is used in the second-line treatment of hospital infections (pneumonia, peritonitis, etc.). complicated urinary tract infections), usually caused by multidrug-resistant gram-negative bacteria,

4th generation cephalosporins. In recent years, the cephalosporin **cefepime** has been synthesized, which has an even broader spectrum in the gram-negative area than 3rd generation cephalosporins, and in its effect on gram-positive bacteria it approaches 1st generation cephalosporins. It is particularly effective against P. aeruginosa and S. aureus, so it is used for severe intrahospital infections with resistant bacteria (pneumonia, sepsis, meningitis, osteomyelitis). It penetrates the blood-brain barrier to the same extent as 3rd generation cephalosporins. The use of cefepime should be avoided in patients with severe renal insufficiency, as encephalopathy may occur.

5th generation cephalosporins. Currently, there is only one representative of this group – **ceftaroline**. In addition to acting on gram-negative enterobacteria (except Pseudomonas) and streptococci as a third-generation cephalosporin, ceftaroline has excellent activity against methicillin-resistant Staphylococcus aureus and enterococci (E. fecalis). This makes it the antibiotic of choice for complicated skin and subcutaneous tissue infections and severe community-acquired pneumonia. Ceftaroline is administered as an intravenous infusion, and is excreted mostly as unchanged drug in the urine.

6th-generation cephalosporins. This generation of cephalosporins also includes only one drug, **cefiderocol**. Cefiderocol is a siderophoric (iron-binding) cephalosporin that is resistant to all types of beta-lactamases, including metallo-beta-lactamases, and is used to treat severe systemic infections (pneumonia, complicated urinary tract infections, sepsis) caused by the most resistant gram-negative bacteria, Acinetobacter, Klebsiella, and Pseudomonas.

Table 32. Daily doses of some cephalosporins
(calculated for a healthy, young man weighing 70 kg).

DRUG	ORAL DOSE	PARENTERAL DOSE
Cefazolin		1- 1,5 g/6 h i.v., i.m.
Cefalexine	1 g/6 h	
Cefuroxima		1,5 g/8 h i.v., i.m.
Cefotaxime		2 g/12 h i.v., i.m.
Ceftriaxone		2 g/24 h i.v., i.m.
Ceftazidima		1 g/8 h i.v., i.m.
Cefepime		2 g/12 h i.v., i.m.

Adverse effects of cephalosporins. The most common adverse effect of cephalosporins is allergy. It has been established that 8-20% of patients allergic to penicillins show the same allergic manifestations after the use of cephalosporins. This is a sufficient reason to avoid the use of cephalosporins in patients allergic to penicillins. Slightly less often, 2nd and 3rd generation cephalosporins show nephrotoxic effects. Therefore, their use together with aminoglycosides should be avoided. Some of the

cephalosporins, which also have a 4-nitrogen ring in their molecule (moxalactam, cefoperazone), have specific adverse effects. They interfere with the synthesis of coagulation factors in the liver, and can lead to bleeding. In addition, they act on alcohol metabolism similarly to disulfiram: they inhibit aldehyde dehydrogenase and cause unpleasant vasomotor symptoms. Therefore, patients must be warned not to drink alcohol during therapy.

Cephalosporins can also cause leukopenia, thrombocytopenia, or hemolytic anemia more often than other antibiotics, on an immunological basis.

Other beta-lactam antibiotics. Recently, antibiotics have been synthesized that have a beta-lactam ring, but they are neither penicillins nor cephalosporins.

Carbapenems. Unlike cephalosporins and penicillins, carbapenems (imipenem, meropenem, ertapenem, and doripenem) have another cycle in their molecule, in addition to the beta-lactam ring, consisting only of C atoms (hence the carba- in the name). Carbapenems are resistant to most beta-lactamases. They are active against most gram-positive (meropenem weaker than imipenem) and gram-negative (meropenem stronger than imipenem) bacteria, including Pseudomonas and some strains of methicillin-resistant staphylococci. They are also very effective against anaerobic non-spore-forming bacteria, including Bacteroides fragilis. However, carbapenems have little or no effect on Enterococci and Acinetobacter. Imipenem is administered only parenterally, in combination with cilastatin, a substance that inhibits renal dipeptidase enzymes (which otherwise degrade imipenem). Cilastatin provides high concentrations of the active drug in the urine. The most common adverse reactions are nausea and vomiting, and convulsions occur in 1% of patients. The dose of imipenem is 500 mg/6 hours i. v. Unlike imipenem, meropenem is not sensitive to the action of dipeptidases, so it is administered alone, without cilastatin. The dose of meropenem is 0.5-1 g/8 hours i.v. Side effects include nausea and vomiting, rash, thrombocytopenia, and liver function disorders. Since meropenem does not cause convulsions, it is the carbipenem of choice for the treatment of bacterial infections of the central nervous system.

Since meropenem and imipenem were widely used in hospitals, carbapenem-resistant strains have developed, which are now the cause of a significant percentage of hospital infections. In order to overcome this problem, combinations of carbapenems with beta-lactamase inhibitors have been created: **imipenem with cilastatin and relebactam** and **meropenem with vaborbactam**. These antibiotics have proven successful in the treatment of hospital-acquired pneumonia caused by multidrug-resistant gram-negative bacteria.

Ertapenem differs from meropenem and imipenem in its slower elimination, which allows for once-daily dosing. The spectrum of action is similar to that of other carbipenems, but it does not act at all on Pseudomonas and Acinetobacter. It is used for mild infections in the abdomen and pelvis that have occurred outside the hospital.

Monobactams. Monobactams also have a beta-lactam ring in their molecule, but they do not have any other ring besides it (hence the name mono). The main representative of monobactams is aztreonam. It is resistant to beta-lactamases of gram-negative bacteria. It does not act on gram-positive and anaerobic bacteria, but is very active against almost all enterobacteria, including Acinetobacter. It is used only parenterally, in the treatment of severe infections with gram-negative bacteria (sepsis, peritonitis, intraperitoneal abscesses, etc.). The dose of aztreonam is 2 g/6 hours i.v. or i.m.

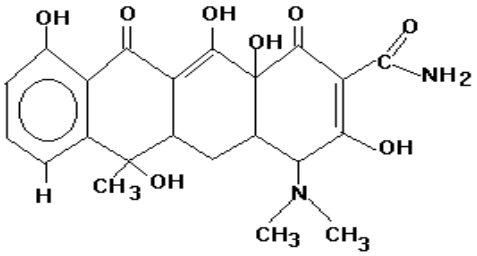
Interestingly, there is no cross-allergy between monobactams and other beta-lactam antibiotics. This means that in case of allergy to penicillins or cephalosporins, aztreonam can be given without danger.

Bacterial resistance to beta-lactam antibiotics

There are several mechanisms by which bacterial cells become resistant to beta-lactam antibiotics: (1) reduced penetration of antibiotics through porins, openings in the outer lipid membrane of gram-negative bacteria; (2) increased release of antibiotics from the periplasm by transport systems in the outer lipid membrane of gram-negative bacteria; (3) modification of penicillin-binding proteins in the bacterial cell wall, so that their affinity for beta-lactam antibiotics is reduced; (4) production of specific enzymes, so-called beta-lactamases, which degrade the beta-lactam ring of these antibiotics. Certainly, the most significant mechanism of resistance is the production of **beta-lactamases**. There are more than 100 species, which are either very specific (so that they degrade only penicillins or only cephalosporins or only some other beta-lactam antibiotics) or have a broad spectrum, so that they degrade almost all beta-lactam antibiotics. Beta-lactamases are divided into four groups: A, B, C and D. Group B beta-lactamases are made up of the so-called metallo-beta-lactamases, to which only one pair of beta-lactam antibiotics (**cefiderocol and aztreonam**) is resistant. Another problem in treatment are bacteria that produce beta-lactamases from **group D** (**OXA-48, OXA-23**), which are only effective against **ceftazidime-avibactam, cefiderocol and aztreonam**. Bacterial resistance to beta-lactam antibiotics can be prevented by choosing the right antibiotic and using it in sufficient doses. Also, the use of a combination of beta-lactam antibiotics with aminoglycosides reduces the possibility of resistance. It is very important to determine the presence of beta-lactamases with an extended spectrum of action by specific tests; in such cases, adequate antibiotics should be used in maximum doses from the beginning of the treatment.

TETRACYCLINES

Tetracyclines inhibit protein synthesis by binding to the 30S subunit of the bacterial ribosome. They are bacteriostatic. They are highly effective against Staphylococcus aureus, pneumococci, and gonococci, but are ineffective against group B and D streptococci. Among gram-negative bacilli, H. influenzae, Campylobacter, Brucella, V. cholerae, Yersinia pestis, Francisella tularensis, Yersinia enterocolitica, and H. dycrei are sensitive to tetracyclines. Tetracyclines suppress the growth of Actinomyces, rickettsiae, chlamydia, mycoplasma, and most spirochetes. Today, they are most commonly used for the treatment of rickettsial infections (spotted typhus, Q fever, etc.), chlamydial genital infections, and for the treatment of pneumonia caused by mycoplasmas. They are also useful for treating more severe forms of acne because they inhibit the growth of Propionbacterium acnes, which is thought to change the consistency of sebum and lead to blockage of the sebaceous gland openings..



TETRACIKLIN

Tetracyclines differ significantly from each other only in their pharmacokinetic characteristics. On the one hand, chlortetracycline, oxytetracycline, demeclocycline and methacycline are poorly absorbed from the digestive tract (from 30% to 80% of the oral dose) and are excreted mainly **via the kidneys**. On the other hand, **minocycline and doxycycline are completely absorbed** from the digestive tract (100% and 95% of the oral dose), and are excreted via the kidneys to a small extent (minocycline) or not at all (doxycycline). The absorption of tetracycline is hindered by aluminum hydroxide, calcium, magnesium, iron salts and bismuth subsalicylate because tetracyclines are chelated with di- and trivalent cations. All tetracyclines penetrate well into all tissues and body fluids. All are at least partially excreted via the bile, undergoing enterohepatic circulation. The latter is especially true for doxycycline, which has the longest half-life. Minocycline stands out from other tetracyclines in its good activity against the multidrug-resistant hospital pathogen Acinetobacter, and is currently the only antibiotic that can be used orally in the treatment of infections with this bacterium.

Table 33. Daily doses of tetracycline in adults.

DRUG	ORAL DOSE	PARENTERAL DOSE
Tetracycline	250- 500 mg/6 h	500 mg/12 h i.v.
Doxycycline	100 mg/24 h	200 mg/24 h i.v.

The side effects of tetracyclines result partly from their direct effects on human cells and partly from their broad antibacterial spectrum. They cause irritation of the gastric mucosa and diarrhea due to the overgrowth of resistant microbial flora in the colon. They lead to photosensitization, and rarely to toxic effects on the liver and kidneys. They should not be used in pregnant women and children under 8 years of age because they are deposited in the teeth and bones. The teeth acquire a yellowish-brown color, and their enamel is less developed. Bone mineralization is disturbed, making them less resistant to mechanical stress. A very specific side effect is caused by minocycline, which causes localized or diffuse hyperpigmentation of the skin or mucous membranes in areas exposed to the sun. This hyperpigmentation resolves after discontinuation of the drug, but recurs in the same place if the patient takes minocycline again. Such a skin change is also called a "fixed rash".

In practice, it is particularly important to know that tetracyclines can reduce the protective effect of oral contraceptives, and that conception is possible despite regular use of contraceptives. Patients should be informed of this fact so that they can adjust their sexual activities or use additional forms of contraception.

Recently, a semi-synthetic derivative of minocycline, **tigecycline**, has also been in clinical use. Tigecycline is administered only intravenously, due to poor absorption after oral administration. It is active against a large number of gram-positive, gram-negative and anaerobic bacteria, with the exception of Proteus and Pseudomonas. Resistance to tigecycline is less common than to other tetracyclines, and this antibiotic has found a place in the treatment of polymicrobial abdominal infections, as well as skin infections. Since it is excreted exclusively in the bile, its dose does not need to be reduced in patients with renal failure. Like other tetracyclines, it causes nausea and vomiting after prolonged use. A new tetracycline for parenteral use is **eravacycline**, which is approved for the treatment of complicated intra-abdominal infections. It is active against many gram-positive bacteria, gram-negative bacteria, and anaerobic bacteria, but is not active against Pseudomonas aeruginosa and Burkholderia cenocepacia.

ERYTHROMYCIN, AZITHROMYCIN AND CLARITHROMYCIN

Erythromycin is one of the macrolide antibiotics (it has a large lactone ring attached to one or more deoxy-sugars). In lower doses it acts bacteriostatically, and in higher doses it acts bactericidally. It reversibly binds to the 50S subunit of the ribosome and thus prevents the synthesis of bacterial proteins.

It inhibits the growth and reproduction of pyogenic streptococcus, pneumococci, sensitive staphylococci, Cl. perfringens, Corynebacterium diphteriae, Listeria monocytogenes. It is generally ineffective against gram-negative bacilli, with the exception of H. influenzae. It is excellently effective against gonococcus, and moderately effective against Borrelia, B. pertussis, P. multocida, B. fragilis, Campylobacter jejuni, M. scrofulaceum and M. kansasii. The good effect of erythromycin on mycoplasmas, chlamydia and Legionella pneumophila is particularly important.

It is administered orally and parenterally, depending on the severity of the infection. It is excreted in its active form in the bile, where it reaches high concentrations. It **does not penetrate the blood-brain barrier well** enough, so it cannot be used to treat infections of the central nervous system.

Erythromycin is the drug of choice for diseases caused by mycoplasmas, chlamydia, and Legionnaires' disease. It is given to penicillin-allergic patients suffering from pneumococcal or streptococcal infections. It is also very effective in eliminating diphtheria bacillus from the pharynx of carriers.

The oral dose of erythromycin is 250-500 mg every 6 hours in a healthy adult.

Adverse effects. Erythromycin estolate can sometimes cause cholestatic hepatitis of a benign course. Epigastric pain, abdominal cramps and diarrhoea are common with all erythromycin preparations. It is particularly difficult to tolerate in children, who usually vomit after oral administration of erythromycin. The basis of these adverse effects is the activation of motilin receptors, which is caused by erythromycin.

Newer macrolide antibiotics. After erythromycin, a large number of macrolide antibiotics were synthesized, some of which are used in practice today: **roxithromycin, clarithromycin, azithromycin and midecamycin**. These drugs remain in the body for a longer time, so they can be administered only once or twice a day. They are better tolerated than erythromycin, because they cause gastrointestinal problems to a lesser extent. Azithromycin remains in the body for a particularly long time, so it is often sufficient to administer it for only three days, in a single daily dose. The spectrum of antibacterial activity of the newer macrolide antibiotics is similar to that of erythromycin.

Fidaxomicin is a macrolide that is not absorbed from the gastrointestinal tract at all after oral administration. It has shown excellent activity against the causative agent of pseudomembranous colitis, the bacterium Clostridium difficile. It is used orally exclusively for the treatment of recurrent diarrhea caused by Clostridium difficile, which no longer responds to metronidazole or vancomycin.

Erythromycin **inhibits the metabolism of other drugs on cytochrome P450** to the greatest extent, and other macrolides to a lesser extent. Therefore, before prescribing any of the macrolides, potential interactions with drugs that the patient is already taking or will take during the administration of macrolides should be carefully checked. Another problem with the use of all macrolides is their tendency to **prolong the QT interval** in the ECG, which predisposes the patient to the development of serious ventricular arrhythmias, especially if he or she is simultaneously taking other drugs with the same side effect (some antiarrhythmics, antipsychotics, antidepressants, quinolone antibiotics, etc.).

KETOLIDES

Ketolides are macrolide-related antibiotics that are synthesized from erythromycin. Only one ketolide, **telithromycin**, has been used to date. Telithromycin acts by inhibiting the formation of the 50S and 30S ribosomal subunits, as well as protein

synthesis on the 50S subunit. Its spectrum of action includes: non-methicillin-resistant Staphylococcus aureus, many types of streptococci, Haemophilus influenzae, Legionella, Moraxella catarrhalis, and some types of chlamydia. Telithromycin has no effect on Enterobacteriaceae, Pseudomonas, and Acinetobacter.

Telithromycin is used to treat mild to moderate community-acquired pneumonia, exacerbations of chronic bronchitis, acute sinusitis, and tonsillopharyngitis that are unresponsive to erythromycin. It is administered orally, once daily.

This antibiotic has many side effects. It can cause cardiac arrhythmias because it prolongs the QT interval, worsens myasthenia gravis, is hepatotoxic, interferes with the accommodation process in the eye, and inhibits CYP3A4, which is why it interacts with numerous other drugs.

CLINDAMYCIN AND LINCOMYCIN

Clindamycin and lincomycin belong to the group of lincosamide antibiotics. **Clindamycin** is better absorbed from the digestive tract, has greater efficacy and fewer side effects than lincomycin. Therefore, lincomycin has become an obsolete (outdated) drug, which is no longer used in practice.

They act in the same way as erythromycin (by binding to the 50S subunit of the bacterial ribosome and inhibiting protein synthesis), against pneumococci, pyogenic streptococcus, S. viridans and staphylococci. They are highly active against Bacteroides fragilis and other anaerobic bacteria. They inhibit the growth of Actinomyces israelii, Nocardia asteroides and Toxoplasma gondii.

Clindamycin is administered both orally and parenterally. The daily dose of clindamycin for an adult is 150-300 mg/6 hours orally, and 300-600 mg/12 hours i.v. or i.m. It penetrates all body spaces, **except the central nervous system**. It penetrates bone tissue and abscess walls especially well.

It is most commonly used for infections with anaerobic bacteria in the abdomen and pelvis and for the treatment of lung abscesses. Clindamycin has shown excellent effects in the treatment of periodontal infections and pharyngeal infections. The combination of clindamycin with some of the aminoglycosides has proven to be justified whenever a mixed infection with both anaerobes and gram-negative bacteria is suspected. Because it is effective against staphylococci and reaches high concentrations in bone tissue, clindamycin is widely used in the treatment of staphylococcal osteomyelitis and arthritis.

A particular problem with the use of clindamycin is the resistance of staphylococci, which can be congenital and acquired. Methicillin-resistant staphylococci (MRSA) should not be treated with clindamycin, as they are generally congenitally resistant to this drug. In congenital resistance, strains are usually simultaneously resistant to both clindamycin and macrolide antibiotics. If staphylococci are isolated before antibiotic therapy is started, clindamycin should be used only if the isolated strain is not resistant to macrolides and if it does not show acquired (inducible) resistance due to the presence of erythromycin, which is checked by the so-called "D-test".

Adverse effects. In 1-10% of patients, clindamycin can cause pseudomembranous colitis, which is sometimes fatal. The cause of colitis is the multiplication of Clostridium difficile in the lumen of the colon, which is resistant to clindamycin. Therefore, as soon as diarrhea occurs, clindamycin should be discontinued and the patient should then be given oral vancomycin or metronidazole.

SPECTINOMYCIN

It is chemically an aminocyclitol. It inhibits protein synthesis in gram-negative bacteria by binding to the 30S subunit of the ribosome. It has a bacteriostatic effect.

It is administered only parenterally because it is poorly absorbed from the digestive tract. Most of it (75%) is eliminated in the urine, unchanged. The entire treatment with spectinomycin is carried out with only one i.m. injection of 2 g.

The only indication for the use of spectinomycin is uncomplicated gonorrhea, but today it is increasingly being supplanted by ceftriaxone even in this use. Sometimes it causes insomnia, fever, nausea and urticaria.

CHLORAMPHENICOL

Chloramphenicol inhibits protein synthesis in bacterial cells by reversibly binding to the 50S subunit of the ribosome. It acts bacteriostatically.

Chloramphenicol has an extremely broad spectrum of action. It acts on almost all gram-negative aerobic bacteria (but weakly on Pseudomonas), on anaerobes, on gram-positive aerobic bacteria (but weakly on Staphylococcus aureus), on rickettsiae and mycoplasmas. **It should not be given in chlamydial infections**, as it even promotes their growth!

It is administered intravenously and orally (it was also administered intramuscularly in the past). It is distributed in all tissues, reaching about 70% of the blood concentration in the central nervous system. It is **inactivated in the liver** by binding to glucuronic acid, and in this form is excreted via the kidneys. Interestingly, chloramphenicol achieves higher blood concentrations after oral administration than after intramuscular administration!

Due to its high toxicity, the use of chloramphenicol should be limited to infections that cannot be reliably treated with other antibiotics. These include: abdominal typhoid; meningitis caused by H. influenzae resistant to ampicillin; meningitis caused by meningococcus or streptococcus resistant to penicillin; brain abscess; severe anaerobic infections; rickettsial infections when tetracyclines cannot be used. The daily dose of chloramphenicol in adults is 500 mg/6 hours, orally or intravenously.

Adverse effects. A few percent of patients receiving chloramphenicol develop dose-dependent anemia, which is fortunately reversible after discontinuation of the drug. However, in a small number of patients (1 in 30,000), chloramphenicol causes an idiosyncratic reaction that leads to damage to all bone marrow lineages. The result is **bone marrow aplasia** with pancytopenia. The incidence of pancytopenia is not related to the dose of the drug, but is higher in patients who receive chloramphenicol repeatedly.

If chloramphenicol is administered to a newborn in large doses, the "**gray baby syndrome**" occurs. The disease begins about the 4th day after the start of the drug. Vomiting, tachypnea, flatulence, cyanosis and rare green stools occur. After 24 hours, the newborn becomes lethargic, his body temperature drops and acidosis develops. About 40% of small patients die. The cause of this syndrome is the immaturity of the newborn's metabolic and excretory mechanisms, which leads to the accumulation of chloramphenicol. In case of urgent need, chloramphenicol can also be used in newborns, but only in small doses and with constant monitoring of the drug concentration in the blood.

AMINOGLYCOSIDES

Aminoglycosides are bactericidal antibiotics. They inhibit protein synthesis in the bacterial cell by interfering with the binding of mRNA to ribosomes. The most commonly used are: **gentamicin, amikacin, streptomycin, tobramycin, kanamycin, netilmicin and neomycin**.

They primarily act on aerobic gram-negative bacilli. Of the gram-positive bacteria, only Staphylococcus aureus and epidermidis are more sensitive to them. They do not act on anaerobic bacteria.

They are only administered parenterally because they are not absorbed from the digestive tract. They do not pass through the blood-brain barrier. They are excreted mostly unchanged via the kidneys.

Aminoglycoside antibiotics are primarily used to treat infections with **gram-negative bacteria** (urinary tract infections, abdominal infections). Streptomycin is currently used only for the treatment of tuberculosis and diseases caused by Pasteurella species (tularemia, plague). Due to its high toxicity, neomycin is used only locally (in the form of an ointment) and orally for preoperative colon preparation. Gentamicin is excreted almost unchanged in the urine, which is why it is suitable for the treatment of urinary tract infections. Amikacin and tobramycin are reserved for infections with bacteria resistant to other aminoglycosides (e.g. Pseudomonas) because they are more resistant to the enzymes that form the basis of bacterial resistance to this group of antibiotics. The newest drug from the aminoglycoside group is **plazomicin**, approved for the treatment of complicated urinary tract infections caused by enterobacteria that produce beta-lactamases from groups A, C and D. All aminoglycosides act synergistically with beta-lactam antibiotics.

Daily doses of some aminoglycosides for adults are: amikacin 15 mg/kg i.m., i.v.; gentamicin 3 mg/kg i.m., i.v.; streptomycin 14-28 mg/kg i.m.; neomycin 1 g/6 hours orally, for preoperative colon preparation. Aminoglycosides should be administered in as few daily doses as possible (preferably one or two), because then their effect on the causative agents of the infection is maximal. The reason for this is the existence of a post-antibiotic effect, i.e. the fact that the effect of antibiotics on bacteria exists even after the concentration of the drug in the blood has decreased to an undetectable level (due to granulocyte stimulation). Also, the toxicity of aminoglycosides is lower if they are administered in fewer daily doses (because toxic effects depend not on the level of concentration in the blood, but on the duration of the presence of drug concentrations in the blood that have the potential to damage the patient's tissues and organs).

The side effects of aminoglycosides are dose-dependent. They accumulate in the peri- and endolymph of the inner ear and vestibular apparatus, leading to progressive destruction of vestibular and cochlear sensory cells. Patients initially experience tinnitus, nausea and vomiting, and then there is a **loss of perception of high-frequency tones**, dizziness and ataxia.

In addition to ototoxicity, aminoglycosides also have **nephrotoxic properties** because they damage the cells of the proximal tubules. This damage to the tubules is most often reversible. Tobramycin is less nephrotoxic than other aminoglycosides.

Of particular importance in anesthesiology is the property of aminoglycosides to act as neuromuscular blocking agents. If administered immediately before general anesthesia, they may potentiate the effects of neuromuscular blocking agents and lead to prolonged muscle paralysis and apnea. In such cases, intravenous calcium should be administered.

SULPHONAMIDES

Sulfonamides are not antibiotics in the strict sense of the word (they are not produced by microorganisms, but are obtained synthetically), but they are described here because of their indispensable role in the treatment of bacterial infections. They are **competitive antagonists of para-aminobenzoic acid**, so they prevent the synthesis of folic acid in the bacterial cell. Since human cells use exogenous folic acid, sulfonamides do not affect them.

Sulfonamides inhibit the growth of pyogenic streptococcus, pneumococcus, Haemophilus influenzae, H. Dycrei, Nocardia, Actinomyces and chlamydia. They act as bacteriostatics.

Sulfonamides differ from each other in their pharmacokinetic characteristics, according to which they are classified into 4 groups. The first group consists of sulfonamides that are **rapidly absorbed and rapidly excreted**, such as sulfisoxazole, sulfadiazine, sulfadimidine, and sulfamethoxazole. The second group consists of drugs that are very **poorly absorbed** from the digestive tract, so they are used to treat diseases of the digestive tube itself. The best-known representative of this group is sulfasalazine. **Sulfonamides for local application** (sulfacetamide, mafenide, silver sulfadiazine) make up the third group, while the fourth group includes drugs that are **rapidly absorbed and slowly excreted** (sulfadoxine, sulfadimethoxine, sulfamethoxypyridazine, and sulfamethoxydiazine). Sulfonamides from the first and fourth groups (except sulfisoxazole) penetrate well into all tissues and body fluids, including the central nervous system. They are mostly acetylated in the liver and excreted in the urine.

Uncomplicated urinary tract infections (most often caused by E. coli) respond well to sulfonamides (sulfisoxazole and sulfamethoxazole). They can also be used for prophylaxis of rheumatic fever relapse (sulfadiazine) as an alternative in patients who are allergic to penicillin. The use of sulfonamides in the treatment of pyogenic infections is severely limited by the inactivation of pus due to the high concentration of amino acids and purine bases. **Mafenide or silver-sulfadiazine**, in the form of creams, are used topically for the treatment of burns. Daily doses of some sulfonamides in adults are: sulfadiazine 1 g/6 hours orally, sulfisoxazole 1 g/6 hours orally, sulfadoxine 500 mg/24 hours orally, and sulfasalazine 1 g/6 hours orally. Only sulfadiazine is currently used parenterally (intravenously); such administration is complicated, because due to its poor solubility, the drug must be dissolved in a large volume of 5% glucose and given in a very slow intravenous infusion.

The side effects of sulfonamides are serious and numerous, so they are **contraindicated in children under 12 years of age**, **at the end of pregnancy and during lactation**. Sulfonamides cause a number of skin changes: photosensitization, exfoliative dermatitis and Stevens-Johnson syndrome (erythema multiforme associated with ulceration of the mucous membranes). Hematological side effects (agranulocytosis, anemia) and nephrotoxicity due to crystallization of the drug in the lumen of the tubules (this can be easily prevented by taking enough fluids and alkalinizing the urine).

A special place in therapy is occupied by the **combination of trimethoprim and sulfamethoxazole** (Bactrim), which can be administered orally and parenterally (most often one tablet contains 400 mg of sulfamethoxazole and 80 mg of trimethoprim, ratio 1:5). Trimethoprim and sulfamethoxazole act synergistically because they sequentially block the synthesis of folic acid. While sulfamethoxazole inhibits dihydropteroate synthase, trimethoprim binds to dihydrofolate reductase. This combination is the drug of choice for: uncomplicated urinary tract infections, acute and chronic prostatitis, pneumonia caused by Pneumocystis, typhoid fever that does not respond to chloramphenicol and ampicillin, and shigellosis. Bactrim can also be used to treat respiratory infections and hospital-acquired infections in seriously ill patients with multidrug-resistant Stenotrophomonas Maltophyllia. The usual dose of Bactrim for adults is 2 tablets every 12 hours. There is also a parenteral form of Bactrim, which can be administered intravenously, in the same dose as orally.

Bactrim is contraindicated in pregnancy and lactation.

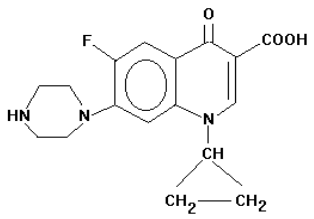
Like sulfonamides, trimethoprim penetrates all tissues, including the brain. Most of the administered drug is eliminated unchanged in the urine.

Side effects of trimethoprim include **thrombocytopenia, leukopenia, and megaloblastic anemia** due to interference with folic acid metabolism in the bone marrow. These adverse effects can be mitigated by the use of folinic acid.

QUINOLONS

Quinolones are synthetic antimicrobial drugs with a very broad spectrum of activity and the possibility of oral administration. They inhibit DNA gyrase, an enzyme that is necessary for the "supercoiling" of bacterial DNA, i.e. for the formation of the bacterial chromosome. At therapeutic concentrations, they have a bactericidal effect.

CIPROFLOKSACIN



Quinolones are usually divided into **non-fluorinated** (also called 1st generation quinolones), which achieve sufficient concentrations to eliminate bacteria only in the urinary tract, and **fluorinated** (or 2nd generation quinolones), which achieve therapeutic concentrations in most tissues. Non-fluorinated quinolones (**pipemidic acid, nalidixic acid**) have been used only as uroantiseptics, while fluorinated quinolones (**ciprofloxacin, olfloxacin, levofloxacin, moxifloxacin**) can be used to treat infections in most tissues and organs. Although fluorinated, norfloxacin does not achieve sufficient concentrations in other tissues, so it is used like 1st generation quinolones, for the treatment of urinary infections. The use of non-fluorinated quinolones in practice has ceased, due to the fact that they were used for mild infections, while they could cause potentially severe side effects: tendonitis with possible rupture, neuropathy, depression, taste and smell disorders. Only norfloxacin is still used as a uroantiseptic from this group.

Quinolones are excellent against E. coli, Salmonellae, Shigellae, Enterobacter, Campylobacter and Neisseria. They are somewhat weaker against Pseudomonas, Enterococcus and Pneumococcus. Methicillin-resistant Staphylococcus responds well to ciprofloxacin, as well as Chlamydia, Mycoplasma, Brucella, Legionella and Mycobacteria. However, all quinolones except moxifloxacin have very little effect on anaerobic bacteria, so if a mixed infection with anaerobic and aerobic bacteria is suspected, an antibiotic effective against anaerobes (clindamycin, metronidazole) should be used in addition to quinolones.

They are well absorbed from the digestive tract, penetrate all tissues (but only fluorinated ones are found in sufficient concentrations) and are largely excreted unchanged in the urine.

Ciprofloxacin and norfloxacin have a very favorable effect on urinary tract infections and prostatitis. Soft tissue and bone infections also respond well to these drugs. Ciprofloxacin is now the drug of choice for diarrhea caused by invasive bacteria (Campylobacter jejuni, Yersinia enterocolitica). The dose of ciprofloxacin is 500 mg/12 hours orally, and 100-200 mg/12 hours as an intravenous infusion; the dose of norfloxacin is 400 mg/12 hours orally.

In the last decade, moxifloxacin and levofloxacin have come into use, which achieve significantly higher concentrations in the respiratory tract than other fluoroquinolones. For this reason, they are more effective than others in the treatment of respiratory infections, and are therefore called "**respiratory quinolones**".

Side effects. Fluoroquinolones are relatively well tolerated. Nausea and mild headache are rare, and sometimes photosensitization and skin rash. They also have a specific side effect on the tendons of the large muscles of the extremities, especially the Achilles tendon, which they make less resistant to stress. If patients are not careful and are exposed to physical exertion, strong muscle contractions can lead to rupture of these tendons. Therefore, patients who are prescribed fluoroquinolones should be warned to avoid physical exertion while taking these drugs and for a few weeks afterwards. Fluoroquinolones should also not be given to people with aortic or other arterial aneurysms, because they lead to remodeling of the connective tissue in the blood vessel wall, **weakening of the wall and sometimes rupture**.

A special problem is the tendency of fluoroquinolones to **prolong the QT interval** and act proarrhythmogenically. Their use should be avoided in people with myocardial diseases, especially in combination with other proarrhythmogenic drugs (e.g. amiodarone).

They are contraindicated in pregnant women, during lactation and in children under 17 years of age because they disrupt the normal growth of articular cartilage. They should also not be given to patients with CNS diseases because they can cause convulsions. They can cause confusion in the elderly. They sometimes cause neuropathy, depression, and loss of taste and smell.

Unfortunately, resistance to fluoroquinolones develops rapidly, even during therapy, especially if the causative agent is Pseudomonas. There is cross-resistance among members of this class of drugs.

POLYMYXIN B AND COLISTIN (POLYMYXIN E)

Polymyxins are peptides by chemical structure. They act only on gram-negative bacteria: Enterobacter, E. Coli, Klebsiella, Salmonella, Pasteurella, Bordetella, Shigella, Acinetobacter and Pseudomonas aeruginosa. Interestingly, they are not active against Proteus species. Since they act as detergents, they increase the permeability of bacterial membranes and thus lead to cell lysis. They only act against gram-negative bacteria because they are the only ones with an outer lipid membrane around the cell wall.

In our country, **colistin (colistimethate)** is used in the form of a preparation for intravenous infusion, primarily in hospital settings for the treatment of systemic infections with resistant strains of Acinetobacter, Klebsiella and Pseudomonas aeruginosa. Colistin is distributed mainly in the extracellular space, and poorly penetrates the central nervous system. If treatment of central nervous system infections is necessary, colistin must be administered intrathecally. Over 80% of the ingested dose of colistin is eliminated by the kidneys, in unchanged form. It is administered in three doses daily, due to its short half-life.

Colistin is highly **nephrotoxic and neurotoxic** (in the central and peripheral nervous system, it can lead to respiratory arrest).

Polymyxins are not absorbed from the digestive tract. Polymyxin B is used only for the local treatment of infections of the skin, visible mucous membranes, eyes and ears.

BACITRACIN

Bacitracin is a polypeptide that inhibits bacterial cell wall synthesis. It is active against: most gram-positive bacteria, most notably Haemophilus, Treponema pallidum, Actinomyces and Fusobacterium. It is used only locally - for infections of the skin, visible mucous membranes and eyes, because systemic administration leads to kidney damage.

Bacitracin is often combined with neomycin in preparations for topical use, because neomycin acts on gram-negative bacteria, and on gram-positive bacteria it acts synergistically with bacitracin. Neomycin is an antibiotic from the aminoglycoside group, which inhibits protein synthesis in the bacterial cell. Bacitracin is not absorbed significantly from the site of application, even when the skin or mucous membranes are damaged; Neomycin can be absorbed more significantly if applied to damaged skin or mucous membranes for a longer period of time, and can then have ototoxic and nephrotoxic effects.

GLYCOPEPTIDE ANTIBIOTICS

The glycopeptide antibiotics include **vancomycin and teicoplanin**. Vancomycin is a polypeptide antibiotic that inhibits bacterial cell wall synthesis, but by a mechanism different from that of penicillin. It is bactericidal against gram-positive bacteria and Clostridium difficile. Its action is particularly useful against staphylococci resistant to other antibiotics (especially methicillin-resistant staphylococcus) and enterococci. It is not absorbed from the digestive tract, so it is administered orally for the treatment of pseudomembranous colitis after antibiotic use (caused by the proliferation of Clostridium difficile; this complication most often occurs after the use of clindamycin), and intravenously for the treatment of systemic infections caused by resistant gram-positive bacteria (primarily staphylococcus). The dose of vancomycin is 125 mg/6 hours orally, and 1 g/12 hours as an intravenous infusion.

The main adverse effects are **ototoxicity and nephrotoxicity**. When administered intravenously, the dose of vancomycin must be diluted in 500 ml of 5% glucose and given slowly, as an infusion lasting at least 1 hour. If vancomycin is administered more quickly, vasoactive mediators are released and redness of the upper half of the body occurs (the so-called red man syndrome). Since the toxicity of vancomycin is directly dependent on its concentration in serum, monitoring of vancomycin concentrations during therapy is recommended in order to prevent the occurrence of adverse effects in time.

Teicoplanin acts by a similar mechanism to vancomycin. Due to its slower elimination, it can be administered only once a day. Teicoplanin can also be administered **intramuscularly**, which is convenient for outpatient therapy. Its spectrum of action is the same as that of vancomycin. Teicoplanin is less nephrotoxic than vancomycin, and does not cause red man syndrome when administered. Teicoplanin does not penetrate the central nervous system, so it cannot be used to treat meningitis and other central nervous system infections.

METRONIDAZOLE

Initially, only the effect of metronidazole on Trichomonas vaginalis, E. hystolitica and G. lamblia was known. Later, it was discovered that it has a strong antibacterial effect on all anaerobic cocci, anaerobic gram-negative bacilli (including Bacteroides) and anaerobic spore-forming gram-positive bacilli. The nitro group of metronidazole takes electrons from electron-transporting proteins in the cell and thus disrupts the synthesis of energy-rich compounds. It has been shown in animals that it can act carcinogenicly, but this has not been proven in humans.

It can be administered both orally and parenterally. It is partially metabolized in the liver and excreted via the kidneys, staining the urine red-brown.

In addition to its use in the treatment of protozoan infections, metronidazole has been used in severe abdominal and pelvic infections caused by anaerobic bacteria. It is also useful in the treatment of pseudomembranous colitis caused by Cl. difficile. The dose of metronidazole is 500 mg/8 hours orally, and 1 g is given as a loading dose intravenously, followed by 500 mg/8 hours.

Adverse effects. The most common adverse effects are headache, nausea, dry mouth, and metallic taste. It sometimes exhibits neurotoxic changes, both in the central nervous system (dizziness, rarely convulsions and ataxia) and in the peripheral nerves (peripheral neuropathy). It has properties similar to **disulfiram**, so patients are prohibited from drinking alcohol during therapy. It should not be used during pregnancy, because it has teratogenic potential.

Metronidazole interacts with a large number of drugs that are metabolized in the liver, inhibiting their metabolism and leading to an increase in the concentration of these drugs in the blood (e.g. carbamazepine, cyclosporine, fluorouracil). Therefore, when prescribing metronidazole, it is imperative to check for possible interactions with drugs that the patient is already taking (see the Summary of Product Characteristics).

STREPTOGRAMINS

Streptogramins are antibiotics that are always used in combination: **streptogramin A (dalfopristin) + streptogramin B (quinupristin)**, in a ratio of 70 : 30.

Streptogramins inhibit protein synthesis in the bacterial cell and have a bactericidal effect on **Gram-positive** bacteria: streptococci and staphylococci, including strains resistant to other antibiotics. They have a bacteriostatic effect on Enterococcus faecium, while they have no effect on Enterococcus faecalis.

They are used to treat infections caused by streptococcus, pneumococcus, staphylococcus and E. faecium that do not respond to other antibiotics.

Streptogramins are administered **intravenously**, in two or three daily doses. They are metabolized in the liver and are mostly excreted in the bile. They inhibit the enzyme CIP3A4, so they can slow down the metabolism of other drugs: warfarin, diazepam, astemizole, terfenadine, cyclosporine, etc.

The most common side effect is muscle and joint pain during and immediately after the infusion.

OXAZOLIDINONES

Oxazolidinones are synthetic antibiotics that act on Gram-positive bacteria (streptococcus, staphylococcus, enterococcus, anaerobic Gram-positive cocci, corynebacteria, Listeria monocytogenes).

The main representative of this group of antibiotics is **linezolid**, which acts by inhibiting protein synthesis in the bacterial cell. It is administered orally or parenterally. It is used to treat infections with Gram-positive bacteria that do not respond to other antibiotics, primarily those caused by vancomycin-resistant enterococcus and staphylococci resistant to methicillin and vancomycin.

A new oxazolidinone is **tedizolid**, which inhibits protein synthesis in the bacterial cell. Tedizolid is active against Gram-positive bacteria, especially streptococci, staphylococci and enterococci. It is currently approved only for the treatment of acute infections of the skin and its adnexa. It is administered both orally and intravenously. Both linezolid and tedizolid inhibit protein synthesis in human mitochondria, resulting in **leukopenia, thrombocytopenia, anemia, neuropathy, and retinopathy after prolonged use**.

DAPTOMYCIN

Daptomycin is a **cyclic lipopeptide** that binds to the bacterial cell membrane and causes depolarization. Depolarization inhibits protein, DNA, and RNA synthesis, leading to bacterial death. Daptomycin is active only against Gram-positive bacteria, primarily staphylococci and streptococci. It is therefore indicated for the treatment of complicated skin and soft tissue infections, right-sided infective endocarditis caused by Staphylococcus aureus, and the bacteremia that accompanies these two diseases.

It is administered as an **intravenous infusion** once daily. It is distributed in the extracellular fluid and only minimally crosses the blood-brain barrier. Daptomycin is not metabolized to any significant extent, and is mostly excreted unchanged in the urine by glomerular filtration.

Unfortunately, daptomycin is a very toxic drug. It often causes muscle pain and an increase in blood creatine phosphokinase, and occasionally myositis that can progress **to rhabdomyolysis**. Therefore, daptomycin should not be used in patients receiving concomitant statins, as the risk of muscle damage is even greater. In addition, liver and kidney function may be impaired, anemia may be increased, and a small number of patients (the exact frequency is unknown) may develop eosinophilic pneumonia.

DALBAVANCIN

Dalbavancin is a **lipoglycopeptide** antibiotic active against gram-positive bacteria, especially methicillin-resistant Staphylococcus aureus (MRSA). Dalbavancin binds to the bacterial cell wall and interferes with transpeptidation and transglycosylation, i.e. prevents its formation. Dalbavancin is administered as **an intravenous infusion**, and only in two doses with an interval of 7 days. This dosing method is due to the slow elimination of the drug (half-life is about 15 days). Dalbavancin is partially metabolized (it is not known where, but not on cytochromes), and both unchanged drug and metabolites are excreted in the urine. For now, it is used only for the treatment of complicated infections of the skin and subcutaneous tissue.

TUBERCULOSIS THERAPY

The causative agent of tuberculosis, Mycobacterium tuberculosis, very quickly acquires resistance to antimicrobial drugs. That is why tuberculosis is treated exclusively with a combination of drugs, the so-called anti-tuberculosis drugs.

Therapy begins with a combination of three or four first-line anti-tuberculosis drugs. These are: isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin.

Isoniazid prevents the synthesis of mycolic acid, an essential component of the cell wall of mycobacteria. It is used (in an oral dose of 15 mg/kg, three times a week) for the treatment of all forms of tuberculosis and for the prevention of tuberculosis in: (1) people living in a household with a tuberculosis patient; (2) people who have not been vaccinated and whose tuberculin test has become positive; (3) people who are immunosuppressed (AIDS, steroid therapy, etc.). When it comes to latent tuberculosis, i.e. there is an infection without symptoms, the use of isoniazid alone for 9 months is indicated. It is well absorbed and penetrates all tissues. It is metabolized by acetylation in the liver. People who slowly acetylate isoniazid may develop peripheral neuritis; this side effect can be prevented by simultaneous administration of vitamin B6 with isoniazid (10 mg/day). In addition, isoniazid can cause chemical hepatitis.

Rifampicin blocks RNA synthesis in mycobacteria. It is used to treat tuberculosis in an oral dose of 600 mg, before meals, three times a week. The doctor should warn the patient that rifampicin stains the urine orange-red! This drug can cause hepatitis and a flu-like syndrome (fever, headache, weakness). Female patients should be warned that rifampicin blocks the effect of oral contraceptives.

The mechanism of action of **ethambutol** is the inhibition of the synthesis of arabinogalactan, also an essential component of the cell wall of mycobacteria. It is used for the treatment of tuberculosis at a dose of 25 mg/kg/day, orally. It can cause inflammation of the **optic nerve**, which is first manifested by impaired color vision. It penetrates poorly into the central nervous system.

Pyrazinamide kills tuberculosis bacilli that are found in macrophages (in the acidic environment of their lysosomes). The dose of pyrazinamide is 2.5 g orally, three times a week. Pyrazinamide is hepatotoxic and can cause hyperuricemia and gout attacks.

Streptomycin is an aminoglycoside that poorly penetrates body membranes, so it acts primarily on mycobacteria in the extracellular space and cavities (dose: 15mg/kg/day i.m. or i.v.).

Initial therapy for tuberculosis lasts 8 weeks. Four drugs are used: **isoniazid, rifampicin, ethambutol and pyrazinamide**. Serum liver enzyme levels should be monitored weekly. After the first 8 weeks, only two drugs, **rifampicin and isoniazid**, are continued for 4 months. The majority of patients will be cured with this therapy. For resistant cases, second-line antituberculosis drugs are used: (1) parenteral preparations (streptomycin, kanamycin, amikacin or capreomycin), (2) quinolones (moxifloxacin, levofloxacin, gatifloxacin, ciprofloxacin and ofloxacin), and (3) orally administered drugs with bacteriostatic effects (ethionamide, prothionamide, cycloserine, para-aminosalicylic acid, terizidone). Kanamycin and amikacin are aminoglycoside antibiotics, while capreomycin is a peptide antibiotic that is toxic to the inner ear and kidneys. **Ethionamide** inhibits protein synthesis in mycobacteria; it penetrates well into all tissues, is metabolized in the liver to active and inactive metabolites; it is hepatotoxic, causes neuropathy, psychotic reactions and encephalopathy, and is therefore administered together with vitamin B6 and nicotinamide. **Prothionamide** has a similar mechanism of action and toxicity to ethionamide. Para-aminosalicylic acid blocks the synthesis of folic acid in mycobacteria; it causes gastritis, diarrhea, arthritis, hepatitis, and blood dyscrasias. **Cycloserine** interferes with the synthesis of the cell wall of mycobacteria and other bacteria because it acts as an analogue of d-alanine, which is otherwise incorporated into the cell wall. Cycloserine penetrates well into most tissues, including the central nervous system; it is excreted mostly unchanged in the urine, and a smaller part of the administered dose is metabolized in the liver. The main side effects of cycloserine are on the central nervous system: in higher doses it can cause delirium or epileptic seizures. **Terizidone** is a combination of two cycloserine molecules; it is as effective as cycloserine, but its neurotoxicity is less pronounced.

The above drugs are never used alone, but in a combination of 3-5 drugs.

THERAPY OF DISEASES CAUSED BY PATHOGENIC FUNGI

Amphotericin B

Amphotericin B is a polyene antibiotic (it has a large ring in the molecule with many double bonds) that binds to the sterol residue in the membranes of fungal cells, increasing their permeability to ions and small molecules. Water enters the fungal cell uncontrollably, it swells and eventually bursts. Amphotericin B is a natural substance synthesized by the actinomycete Streptomyces nodosus.

The spectrum of action of amphotericin B includes the following types of fungi: Candida, Cryptococcus neoformans, Blastomyces derma-titidis, Histoplasma capsulatum, Torulopsis glabrata, Coccidioides immitis, Paracoccidioides brasiliensis, Sporotrix schenckii, Aspergillus and the causative agents of mucormycosis. Resistance to amphotericin B can develop, but this is not common.

It is poorly absorbed from the digestive tract, so it is administered only intravenously. About 90% of the drug in the blood is bound to plasma proteins. It penetrates well into most tissues and body fluids, but poorly crosses the blood-brain barrier. Amphotericin B is metabolized in the liver and excreted mainly via the bile. Only 5% of the administered dose is excreted as unchanged drug in the urine. Elimination of the drug is slow, biphasic: the half-life in the first phase is one day, and in the second phase 15 days.

Amphotericin B is administered intravenously for the treatment of candidiasis, mucormycosis, invasive aspergillosis, extracutaneous sporotrichosis, cryptococcosis, paracoccidioidomycosis, coccidioidomycosis, and histoplasmosis. The dose of amphotericin B is 0.25-0.6 mg/kg i. v.

Side effects of amphotericin B include pyrexia, azotemia due to toxic effects on renal tubules, and anemia due to inhibition of erythropoietin synthesis in the kidney. Tubular damage is reversible if the drug is discontinued in time. Thrombophlebitis usually occurs at the site of infusion of this drug.

To reduce the toxicity of amphotericin B, a preparation has been developed in which amphotericin molecules are enclosed in tiny phospholipid spheres: liposomes. Liposomal amphotericin B is significantly more expensive, but side effects are much less common than with regular amphotericin B.

Nystatin

Nystatin is also a polyene antibiotic, which acts on fungi by the same mechanism as amphotericin B. Its spectrum of action is similar to that of amphotericin B, but it is used clinically only for the treatment of local candidiasis. It is too toxic for systemic use (nephrotoxicity); it is used only locally, for candidiasis of the oral cavity, intestinal tract, vagina or skin. After local application, it is not absorbed into the blood, so there are practically no side effects.

For the treatment of candidiasis of the gastrointestinal tract, nystatin is administered in an oral dose of 1,000,000 IU/8 hours.

Flucytosine

Flucytosine is converted in fungal cells to 5-fluorouracil, which interferes with the synthesis of RNA and DNA (it inhibits the enzyme thymidylate synthase, so that there is not enough thymidine, which is necessary for DNA synthesis). It is active against Cryptococcus neoformans, Candida, Torrulopsis glabrata and the causative agent of chromomycosis.

Cryptococcus and Candida can develop resistance to flucytosine during therapy, which is the cause of relapse of the disease after initial improvement. Due to the high frequency of resistance, flucytosine is used alone only in the treatment of chromoblastomycosis. For other fungal infections, it is used only in combination with amphotericin B. The dose of flucytosine is 150-200 mg/kg per day, divided into 4 oral doses.

Flucytosine is rapidly and completely absorbed from the digestive tract. It penetrates well into all tissues and body fluids, including the central nervous system. About 80% of the drug dose is excreted unchanged in the urine. The half-life is 3-5 hours. Flucytosine can cause bone marrow depression and liver damage, especially in patients with AIDS.

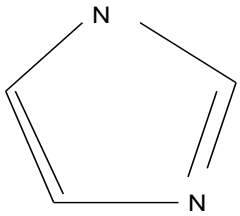
Echinocandins

Caspofungin, micafungin, and anidulafungin are members of a new class of antifungal drugs that inhibit the synthesis of the glucan component of the fungal cell wall. Caspofungin is used to treat imidazole-resistant Candida strains (usually non-albicans strains) and to treat infections caused by Aspergillus. It is administered intravenously and is almost completely metabolized in the liver (but very slowly). Caspofungin is generally well tolerated, although nausea, vomiting, fever, flushing, anemia, and liver damage may occur rarely. Unlike imidazoles, it has very few interactions with other drugs. Anidulafungin and micafungin have slightly fewer side effects than caspofungin, and they interact even less frequently with other drugs. Anidulafungin has a longer duration of action than the other two echinocandins, and is the only one that is degraded by spontaneous hydrolysis in the reticuloendothelial system. Micafungin and anidulafungin are approved for use in very young children.

Because of their poor blood-brain barrier penetration, caspofungin, micafungin, and anidulafungin **cannot be used to treat candidiasis of the central nervous system**.

Imidazole

All compounds in this group contain an imidazole ring in their molecule. Imidazoles interfere with the synthesis of ergosterol, which is essential for the integrity of the fungal membrane. They are highly active against many known pathogenic fungi; moreover, the occurrence of resistance is rare.



Имидазолски прстен

Some of the imidazoles are used only locally due to their high toxicity (**clotrimazole, econazole**), while others are used both systemically and locally (**ketoconazole, miconazole**).

Ketoconazole is administered orally, but its absorption is relatively poor; it does not reach fungicidal concentrations in serum. A necessary prerequisite for its absorption is normal gastric acidity, so H2 receptor blockers and antacids can significantly reduce the bioavailability of an oral dose of ketoconazole. It is almost completely metabolized in the liver, and its metabolites are excreted in the bile. Ketoconazole is used to treat non-meningeal blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, chronic mucocutaneous candidiasis, and disseminated forms of dermatophyte infections (trichophytosis, epidermophytosis, microsporia), but only on condition that the infections are mild and that the central nervous system is not affected.

Miconazole also acts on the same pathogens, but it can only be administered intravenously, because just 10% of the ingested drug is absorbed from the gastrointestinal tract. Miconazole also penetrates poorly into the central nervous system. The dose of ketoconazole is 200-400 mg per day, in a single oral dose. The dose of miconazole is 800 mg/8 hours, in the form of a slow intravenous infusion.

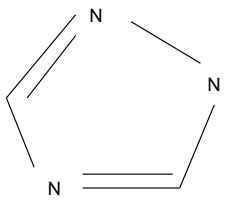
In addition to nausea, anorexia and vomiting, which occur in about 20% of patients, ketoconazole, due to inhibition of steroid hormone synthesis, leads to a number of endocrine disorders in about 10% of patients: amenorrhea, gynecomastia, oligospermia, Addison's disease. Hepatitis may develop in a small number of patients (1: 12,000). On the other hand, miconazole can cause vomiting or even cardiac arrest if administered rapidly intravenously; therefore, it should be given as an infusion lasting at least 1 hour. Miconazole also has serious central neurotoxic effects: tremor, confusion, hallucinations.

Clotrimazole and econazole are used only topically, for the treatment of skin infections caused by dermatophytes (epidermophytia, trichophytia, microsporia), candida or Pityriasis versicolor.

Ketoconazole has significant interactions with many drugs that are metabolized by the same cytochrome P450 enzyme in the liver. Thus, rifampicin and isoniazid reduce the concentration of ketoconazole in the blood, and ketoconazole increases the concentration of warfarin and sulfonylurea derivatives.

Triazoles

Triazoles (**fluconazole, itraconazole, voriconazole, posaconazole**) are closely related to imidazoles. They act by the same mechanism as imidazoles, and have a similar spectrum of action. They are effective against: Candida, Coccidioides immitis, Cryptococcus neoformans, and Histoplasma capsulatum. In addition, fluconazole inhibits the growth of Blastomyces dermatitidis, and itraconazole inhibits the growth of Aspergillus and Sporotix schenckii. Instead of the imidazole ring, they have a triazole ring in their molecule. **Fluconazole penetrates the central nervous system well,** so it is used to treat cryptococcal meningitis and systemic candidiasis. On the other hand, itraconazole poorly crosses the blood-brain barrier and is used primarily for sporotrichosis, coccidioidomycosis, chromomycosis, generalized forms of dermatophytosis, pityriasis, and for oropharyngeal and vulvovaginal candidiasis. The dose of fluconazole is 100 mg daily, orally or intravenously. The dose of itraconazole is 100-200 mg daily, orally.



Triazole ring

Fluconazole causes headache, vomiting, and diarrhea in about 1-4% of patients. Mild, subclinical liver damage with elevated transaminases may sometimes occur. Itraconazole causes similar effects, but its use is contraindicated in pregnancy (because it has shown teratogenic effects in rats). In addition, itraconazole can damage the **myocardium and lead to heart failure**, so it is not a good choice for people with heart disease.

Fluconazole is excreted unchanged in the urine, while itraconazole is metabolized in the liver to inactive metabolites that are excreted in the urine or bile.

Voriconazole is a newer triazole with very good activity against invasive aspergillosis and serious fungal infections caused by Scedosporium apiospermium and Fusarium species. The drug can be administered intravenously and orally. Voriconazole is currently the drug of choice for pulmonary aspergillosis.

Like other azoles, voriconazole is metabolized via the CYP3A4 isoform of cytochrome P450, inhibiting the metabolism of other drugs that use the same enzyme (terfenadine, astemizole, cisapride, pimozide, quinidine). Therefore, signs of overdose with

the latter drugs may occur (prolongation of the QT interval in the ECG). In addition, voriconazole **blurs vision** and causes photophobia; therefore, patients taking it should not drive or operate machinery. Fever and liver damage have rarely been reported with voriconazole.

Posaconazole also inhibits ergosterol synthesis, and is active both in vitro and in vivo against Aspergillus, Candida, Coccidioides immitis, Fonsecaea pedrosoi (chromoblastomycosis), and Fusarium. It is used to treat infections with these fungi, mainly in situations where they are resistant to other antifungals. It is also given for the prophylaxis of fungal infections in patients with acute myelogenous leukemia or myelodysplastic syndrome who are receiving chemotherapy. The main side effects of posaconazole are gastrointestinal complaints, increased body temperature and increased bilirubin. The newest triazole is **isavuconazole**, which is used to treat aspergillosis and mucormycosis. It penetrates well into all tissues, is metabolized in the liver by cytochromes. Unlike other imidazoles, it does not prolong the QT interval, but rather shortens it. It is as effective in the treatment of aspergillosis as voriconazole, and has fewer side effects, which are mainly reduced to an increase in liver enzymes in the serum.

Allylamines

The most important representative of allylamines is **terbinafine.** This drug can be administered orally or topically to the skin. Terbinafine inhibits the enzyme **squalene epoxidase**, thereby preventing the synthesis of ergosterol in the fungal membrane. It is primarily effective in the treatment of epidermophytosis (which cause fungal infections of the skin and nails), while it has little effect on candida. The most important side effect of terbinafine is chemical hepatitis.

Griseofulvin

Griseofulvin is an antibiotic used to treat dermatophytes (epidermophytia, trichophytia, microsporia). It has the unusual property of binding to the keratin of the skin and its adnexa. Fungi feed on keratin and thus ingest griseofulvin in large quantities. Griseofulvin binds to the **microtubules** of fungal cells, disrupting their numerous functions (transport through the cytoplasm, division spindle), which ultimately leads to the death of the parasite. The dose of griseofulvin is 125 mg/6 hours, orally.

Griseofulvin often causes a transient **headache, and can sometimes lead to leukopenia and liver damage**. Since it must be used for several months to treat fungal infections of the hair and nails, it is necessary to periodically monitor the blood count and parameters of liver cell damage (transaminases) in patients. The drug is **teratogenic**, so its use is contraindicated during pregnancy. The patient should be warned not to drink alcohol during therapy with griseofulvin, because griseofulvin has a disulfiram-like effect.

Drugs for local therapy of dermatophytes

Often, a fungal infection affects only a limited area of the skin. In this case, it is sufficient to apply an antifungal drug locally, in the form of a cream, lotion or ointment. **Imidazoles** (econazole, clotrimazole, miconazole), **terbinafine, ciclopirox olamine, haloprogin, tolnaftate** can be applied locally. The effectiveness of these drugs is very similar, and the side effects are minimal. They all work well on pityriasis, although for its treatment it is enough to apply only a keratolytic (10% salicylic acid ointment).

A special problem is the local treatment of **onychomycosis**, due to the poor penetration of antifungal drugs through the nail plate. Until recently, local therapy was ineffective, but in recent years, three drugs have appeared that have excellent penetration through the nail plate and, after local application, achieve a cure in about 80% of patients. These are **tavaborole, amorolfine and elfinaconazole**. Tavaborole inhibits the synthesis of transporting RNA in fungal cells, and amorolfine and elfinaconazole inhibit the synthesis of ergosterol. Their wider application is currently limited by their high cost.

ANTIVIRAL MEDICINES

Viruses are intracellular parasites that use the building blocks of the host cell for their replication. Some of the enzymes required for replication are synthesized based on information from viral DNA or RNA (depending on whether they are DNA or

RNA viruses), which means that they are virus-specific. These enzymes are the site of action of the largest number of antiviral drugs.

Viruses consist of one or two strands of nucleic acid, surrounded by a protein coat, called a capsid. Depending on whether they contain DNA or RNA, viruses are divided into DNA and RNA viruses. **Pathogenic RNA viruses** are: **arborviruses** (causes yellow fever and tick-borne encephalitis), **arenaviruses** (causes meningitis and Lassa fever), **hepacivirus** (causes hepatitis C), **orthomyxoviruses** (causes influenza), **paramyxoviruses** (causes mumps and measles), **picornaviruses** (causes respiratory infections, meningitis, poliomyelitis), **rhabdoviruses** (causes rabies), **rubella virus** (causes rubella) and **retroviruses** (causes AIDS). **Pathogenic DNA viruses** are: **adenoviruses** (causes conjunctivitis and respiratory infections), **hepadnaviruses** (causes hepatitis B), **herpesviruses** (causes cold sores and genital herpes, herpes zoster, chickenpox and cytomegalovirus infections), **papillomaviruses** (causes warts) and **poxviruses** (causes smallpox).

Virus replication in a host cell proceeds through the following stages: (1) binding to and penetration of the cell; (2) removal of the protein coat ("uncoating" of the nucleic acid); (3) synthesis of the components of the virus; (4) assembly of the virus particle ("coating" of the nucleic acid), and (5) release from the host cell. DNA viruses synthesize their components by using their DNA as a template for tranporting RNA, which encodes the synthesis of viral proteins on the host cell ribosomes. RNA viruses do this in several ways: their RNA can be a direct template for transporting RNA, or the viral RNA acts as a transporting RNA, or DNA is created from the viral RNA (using the enzyme reverse transcriptase), which then serves as a template for the synthesis of transporting RNA.

MEDICATIONS FOR HERPES VIRUS INFECTIONS

Infections with Herpes simplex virus (type 1 - the causative agent of herpes labialis, type 2 - the causative agent of herpes genitalis), which is a DNA virus, can be treated with systemic administration of **acyclovir or vidarabine**. Both drugs are analogues of the purine nucleosides guanosine and adenosine, respectively, which are phosphorylated to triphosphate in the host cell and then inhibit viral DNA polymerase. The viral enzyme thymidine kinase (which is necessary for the phosphorylation of acyclovir) has a much higher affinity for acyclovir triphosphate than human thymidine kinase; therefore, acyclovir accumulates in virus-infected cells.

Vidarabine was the first drug used to treat herpetic encephalitis (10 mg/kg/day, as an intravenous infusion lasting 12 hours) and neonatal disseminated herpes. It is less effective than acyclovir in the above-mentioned indications, and has significant toxicity: liver damage, confusion, thrombocytopenia and/or anemia. Therefore, vidarabine is currently mainly used topically, in the form of an eye ointment, for the treatment of keratoconjunctivitis caused by herpes virus type 1. In some patients, this drug irritates the eye, causing burning, tearing, pain and photophobia. **Acyclovir is used primarily for generalized herpes virus infections**, for severe, recurrent genital herpes infections, but also for herpes zoster virus infections (only in severe cases of chickenpox or herpes zoster). After oral administration, acyclovir is incompletely absorbed. About 20% of the drug in serum is bound to plasma proteins; acyclovir penetrates well into all tissues and body fluids, including the placenta, amniotic fluid and milk. Acyclovir is excreted by the kidneys (by glomerular filtration and tubular secretion), mostly unchanged. It remains in the body for a relatively short time: the half-life is only 3-4 hours.

Acyclovir is generally well tolerated, and in most patients causes only headache, nausea and diarrhea. A small number of patients will also experience fatigue, fever, depression, confusion, convulsions and alopecia. When administered intravenously, acyclovir can have a nephrotoxic effect, especially if the patient has a history of kidney disease. To avoid this, the patient should be **well hydrated**. In immunocompromised patients, acyclovir can cause the appearance of platelet microthrombi, which manifests as potentially fatal thrombotic thrombocytopenic purpura or hemolytic uremic syndrome. Acyclovir is not teratogenic or embryotoxic.

The dose of acyclovir is 200 mg/12 hours orally, or 15 mg/kg/day intravenously.

Since acyclovir is poorly and irregularly absorbed after oral administration, **valacyclovir**, a prodrug that is well absorbed and then converted to acyclovir in the liver and intestinal wall, has been synthesized. In this way, serum concentrations of acyclovir are achieved 3 to 5 times higher than those obtained with the administration of acyclovir alone. Valacyclovir has the same side effects as acyclovir; its main advantage is its less frequent dosing (500 mg is given every 12 hours, orally). Valacyclovir is used to treat recurrent genital herpes and moderate-severe forms of herpes zoster.

Herpes simplex eye infection can also be treated with local application of **idoxuridine**, which is too toxic for systemic administration. Idoxyuridine also inhibits DNA polymerase. **Trifluridine** is another drug that is also used topically for the treatment of keratoconjunctivitis caused by herpes viruses types 1 and 2. It is a fluorinated pyrimidine nucleoside that, after phosphorylation, inhibits the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate, and then competes

with deoxythymidine triphosphate for incorporation into viral and host cell DNA. Both drugs can cause corneal clouding after prolonged use.

In the last decade or so, a number of drugs have been approved for use that inhibit viral DNA polymerase. Some of them (famciclovir, penciclovir) require the presence of viral thymidine kinase to become active in the infected cell, while some do not (foscarnet, cidofovir).

Penciclovir is an acyclic guanosine analogue that acts by the same mechanism as acyclovir on the synthesis of herpes virus DNA. ***Famciclovir*** is a prodrug (diacetyl ester of penciclovir), which is converted in the liver to penciclovir after absorption. Penciclovir is used only locally, for the treatment of herpes on the lips. Famciclovir is used systemically, which is well absorbed after oral administration, and provides a bioavailability of penciclovir of 77%. Like acyclovir, penciclovir is slightly bound to plasma proteins (20%) and penetrates well into all tissues. It is eliminated by the kidneys, as an unchanged drug, by glomerular filtration and tubular secretion. Famciclovir is used for the same indications as valacyclovir; it has been shown to lead to a faster cessation of pain in herpes zoster than acyclovir (famciclovir dose: 500mg / 8 hours, orally). Famciclovir can cause confusion and **hallucinations**, and rarely bone marrow suppression. Animal experiments have shown a carcinogenic effect of famciclovir, as well as an inhibitory effect on spermatogenesis.

Since acyclovir, valacyclovir, and famciclovir require viral thymidine kinase, if resistance to one of them occurs due to a mutation in the gene encoding this enzyme, the virus also becomes resistant to the other two drugs (cross-resistance). There is no cross-resistance with foscarnet and cidofovir.

Cidofovir is an acyclic cytosine analog that, after intracellular conversion to cidofovir diphosphate, inhibits the activity of viral DNA polymerase. Since its conversion occurs under the action of host cell enzymes, not viral enzymes, the active form of the drug is found in the same concentrations in infected and uninfected cells.

Cidofovir is poorly absorbed, so it can only be administered intravenously. It is rapidly excreted unchanged in the urine (half-life 2.5 hours), but remains inside cells for a much longer time (several days), bound to phosphocholine. It is used to treat herpes simplex infections that are resistant to acyclovir, for the prevention and treatment of cytomegalovirus retinitis in people with AIDS (5mg/kg intravenously, once a week), for the treatment of condylomas (Condylomata accuminata) and Molluscum contagiosum, and for the treatment of multifocal leukoencephalopathy associated with polyomavirus.

Cidofovir is a nephrotoxic drug, because during tubular secretion it damages the tubule cells, leading to proteinuria, glycosuria, increased creatinine, and sometimes Fanconi syndrome. Cidofovir also relatively commonly causes anterior uveitis and neutropenia; decreased intraocular pressure and metabolic acidosis may occur rarely. Cidofovir has shown carcinogenic, embryotoxic, and teratogenic effects in animal experiments.

Fanconi syndrome refers to a generalized disorder of the functioning of the proximal tubule of the nephron, manifested by hypophosphatemia, decreased serum uric acid levels, proximal tubular acidosis, and the appearance of protein and glucose in the urine.

Note: acyclovir, penciclovir, and cidofovir are secreted in the renal tubules by the same transport system as probenecid; this drug may inhibit their secretion and increase the concentration of these antiviral drugs in the blood.

Foscarnet is an inorganic compound, an analogue of pyrophosphate, which non-competitively inhibits viral DNA polymerase. After oral administration, it is poorly absorbed, so it is administered only intravenously. It binds to plasma proteins to a small extent, and penetrates well into many tissues and body fluids (e.g., the vitreous humor of the eye). It accumulates especially in the bones, as a result of which it is slowly eliminated from the body (retained for several days), as an unchanged drug in the urine.

Foscarnet is used to treat cytomegalovirus retinitis in patients with AIDS, and to treat herpes virus or varicella-zoster virus infections resistant to acyclovir in immunocompromised individuals.

Foscarnet is a nephrotoxic drug, which therefore leads to disturbances in serum mineral homeostasis: hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia. Decreased concentrations of potassium, calcium, and magnesium can cause tetany, paresthesias, arrhythmias, or convulsions. The nephrotoxic effect can be largely prevented by good hydration of the patient. Due to the high concentration it achieves in the urine, foscarnet can cause ulcerations of the external genitalia.

Docosanol is another drug used to treat herpes simplex virus infection. It is a long-chain, saturated alcohol that prevents the virus from entering cells by inhibiting the fusion of the viral envelope with the host cell membrane. It is used exclusively locally for cold sores. There are no side effects, so it is available without a prescription. Docosanol is effective only if applied in the prodromal phase, before the vesicles have yet to erupt.

Cytomegalovirus infections are particularly severe in newborns who acquire them from their mothers during intrauterine life. Most organs are damaged, especially the central nervous system. Cytomegalovirus infections respond well to ganciclovir,

another acyclic guanosine analogue that, after phosphorylation, inhibits the viral DNA polymerase. Ganciclovir requires phosphorylation by the viral protein kinase pUL97 to become active upon entry into the cell. Therefore, ganciclovir triphosphate is concentrated in cells infected with cytomegalovirus.

Ganciclovir is very poorly absorbed after oral administration (6-9%), so it is most often administered intravenously. **Valganciclovir,** a prodrug that is well absorbed and then rapidly converted to ganciclovir in the liver, giving ganciclovir a bioavailability of about 60%, is more commonly used orally. Ganciclovir penetrates well into all tissues, especially the eye. It is not metabolized; it is excreted unchanged in the urine, by glomerular filtration and tubular secretion.

Ganciclovir is used for the treatment of cytomegalovirus retinitis in immunocompromised individuals, and for the prevention of cytomegalovirus infection in patients who have had an organ transplant. The most pronounced side effect of this drug is **bone marrow suppression;** Neutropenia and anemia occur in 30% of patients, and thrombocytopenia in 10%. The teratogenic and carcinogenic effects of ganciclovir have also been shown in animal experiments. Zidovudine, a drug for AIDS, potentiates the myelosuppressive effects of ganciclovir. The dose of ganciclovir is 5 mg/kg/day intravenously for 14 days, followed by maintenance therapy of 5 mg/kg/day every other day.

For the treatment of cytomegalovirus retinitis, **fomivirsen,** a so-called "antisense" oligonucleotide, is used locally. Fomivirsen is complementary to the IE2 region of cytomegalovirus transfer RNA (tRNA). When it binds to tRNA, fomivirsen prevents the synthesis of viral proteins, and thus their reproduction. The drug is injected directly into the vitreous of the eye, and is used to treat cytomegalovirus retinitis in patients with AIDS who have not responded to other therapy. In about 25% of patients, fomivirsen can cause iritis.

Other antiviral drugs

Infections with most RNA viruses, respiratory syncytial virus infection, hepatitis C virus infection (but only in combination with interferon alpha), viral hemorrhagic fever, and Lassa fever can be treated with **ribavirin.** Ribavirin is a guanosine analog that interferes with the synthesis of viral RNA. It also causes mutations in viral RNA, resulting in virions that are unable to replicate.

Ribavirin is used as an **aerosol and orally**. It is well absorbed, with a bioavailability of 64%, and can be increased if the drug is taken with a fatty meal. Ribavirin is metabolized in the liver to a triazole carboxyl metabolite, which is eliminated in the urine along with the unchanged drug. The drug also accumulates in erythrocytes.

In the treatment of respiratory syncytial virus infection, ribavirin is administered in the form of an aerosol, while for other infections it is used orally. After administration by aerosol, deterioration of lung and heart function may occur, while **hemolytic anemia** often occurs after oral administration. When administered together with interferon alpha, ribavirin potentiates its side effects: fatigue, insomnia, depression, pancreatitis. Ribavirin is **mutagenic, teratogenic and embryotoxic**. It is contraindicated in people with sickle cell anemia and hemoglobinopathies.

Smallpox (Variola vera) can be alleviated by the administration of **metisazone** at the beginning of the disease. Metisazone prevents the assembly of the virus after the synthesis of viral DNA, and thus its multiplication. The dose is 3 g/day, orally.

Antibodies can also be used in the treatment of viral infections: gammaglobulin and hyperimmune gammaglobulin. **Gamma-globulin** is a globulin preparation obtained from the serum of blood donors, and **hyperimmune gammaglobulin** is obtained from the serum only of people who have had certain infectious diseases or have been vaccinated against them (e.g. cytomegalovirus, hepatitis B, rabies, varicella-zoster, respiratory syncytial virus). The titer of specific antibodies against certain viruses is much higher in hyperimmune gammaglobulins. Of the antibodies, gammaglobulins and hyperimmune gammaglobulins contain the most IgG type, while IgA and IgM types are found only in impurities. Antibodies from these preparations bind to viruses, preventing their entry into the host cell. They also activate complement and stimulate cellular immunity. These medicinal preparations are most effective if they are administered at the beginning of the disease. Globulins are administered intramuscularly or intravenously. After administration, their protective effect lasts for 2-3 weeks. They are used for the prevention and treatment of those viral diseases against which they contain a sufficient titer of antibodies.

There are several dangers associated with the use of gamma globulin. First of all, there is the possibility of an allergic reaction, which is more common in people who have previously had hypo- or agamaglobulinemia, with repeated administration and with intravenous administration. Intravenous administration of gamma globulin should be slow, otherwise facial flushing, dizziness, drop in blood pressure, palpitations, difficulty breathing and abdominal cramps may occur. Since they are made from human blood, globulin preparations always carry a certain risk of transmitting pathogenic microorganisms and infection (e.g. hepatitis B, C or AIDS viruses). High doses of gamma globulin can cause **aseptic meningitis** in some patients. Finally, gammaglobulins interfere with the development of active immunity after vaccination, so vaccination should be postponed after their administration.

Interferons are regulatory proteins (cytokines) that are produced in the body as a result of viral infection. There are three types of interferons: interferon alpha (type 1, produced mainly in leukocytes), interferon beta (type 1, produced mainly in fibroblasts) and interferon gamma (type 2, produced by killer cells and T lymphocytes). Interferons do not act directly on viruses, but trigger a series of mechanisms that interfere with the reproduction of viruses. They bind to membrane receptors and trigger at least two signaling mechanisms: activation of cellular ribonucleases that degrade single-stranded viral RNA and induction of protein kinases that inactivate the synthesis of viral proteins. Interferons are administered as such, or conjugated with monomethoxy polyethylene glycol (**PEG – pegylated interferons**). Both types of preparations are administered parenterally. When administered subcutaneously or intramuscularly, unconjugated interferons remain in the blood for up to 36 hours; when pegylated interferons are administered in the same way, they remain in the blood for longer, up to 72 hours. Interferons are removed from the blood by degradation in the liver and kidneys.

Alpha interferons are used to treat chronic hepatitis B and C, hairy cell leukemia, Kaposi's sarcoma that occurs as part of AIDS, chronic myeloid leukemia, malignant melanoma, Hodgkin's lymphoma, and genital warts. In the treatment of hepatitis C, alpha interferon is combined with ribavirin. Interferon beta is used in the treatment of multiple sclerosis, while interferon gamma is used to alleviate infections that occur in chronic granulomatous disease, and to slow the progression of malignant osteopetrosis.

Interferons have a large number of side effects. In more than 50% of patients, they cause a **flu-like syndrome** (fever, fatigue, myalgia, arthralgia), but tolerance often develops after repeated doses. There are significant side effects on the central nervous system: **depression** with suicidal tendencies, **impaired memory and concentration**, **insomnia and anxiety**. Bone marrow suppression, gastrointestinal complaints (vomiting, diarrhea, anorexia), hair loss, decreased fertility are also common. Rarely, kidney damage with nephrotic syndrome, lung damage (infiltrates, pneumonitis), increased serum liver enzymes and cardiovascular effects (arrhythmias, cardiomyopathy, myocardial infarction) may occur.

Lamivudine is a cytidine analogue that, after phosphorylation in the cell, inhibits the DNA polymerase of the hepatitis B virus and the reverse transcriptase of the AIDS virus. Therefore, it is used to treat hepatitis B and AIDS. Since the AIDS virus quickly acquires resistance to lamivudine, it is always used in combination with other drugs in this disease.

Lamivudine is well and rapidly absorbed after oral administration (bioavailability 90%), and is excreted unchanged in the urine. It has few side effects, the most significant of which is an **increase in the level of alanine aminotransferase (ALT), creatine kinase and lipase in serum**. It can cause pancreatitis in children.

Remdesivir is a prodrug from which an adenosine analogue is formed in the body that inhibits the RNA polymerase of the SARS-CoV-2 coronavirus. This drug is effective in treating severe forms of COVID-19 (coronavirus infection 19), as it shortens the time to recovery, and in certain subgroups of patients (e.g. those requiring oxygen therapy) it also reduces mortality. Remdesivir is administered intravenously, 100mg once daily for 5 days; it is generally well tolerated, the most common side effects are increased serum transaminases and nausea.

For the treatment of mild to moderate forms of COVID-19 in people with risk factors for developing a severe form, the combination of **nimratrelvir and ritonavir** or monotherapy with **molnupiravir** is used. All three drugs are administered orally. Nirmatrelvir is a protease inhibitor of the virus that interferes with its replication, while ritonavir inhibits cytochromes and thus slows down the metabolism and elimination of nirmatrelvir (therefore, it only serves to increase the concentration of nirmatrelvir in the blood. This combination can reduce the incidence of severe forms of the disease by 88%. The main side effect is liver damage. Molnupiravir is a nucleoside analogue that leads to errors in viral replication. Molnupiravir reduces the incidence of severe forms of COVID-19 by about 30%. **It can impair the growth of bones and cartilage**, so it is not used in people under 18 years of age; it is also not used in pregnancy, because it is teratogenic. **Palivizumab** is a humanized monoclonal antibody against the F-protein on the surface of respiratory syncytial virus (RSV). It contains 95% human and 5% murine amino acid sequences. It neutralizes the virus and prevents its binding to host cells. It is used only for the prophylaxis of RSV infection, during the winter season, as intramuscular injections once a month. It is used only in children at high risk: children under 2 years of age with chronic lung disease and premature children up to 12 months of age. It is well tolerated; so far, only mild redness and pain at the injection site have been described.

Humanized monoclonal antibodies are obtained in the following way: (1) a mouse is immunized with the antigen against which we want to obtain a monoclonal antibody; (2) mouse B lymphocytes are isolated from its spleen and lymph nodes; (3) these lymphocytes are fused with human plasmacytoma cells, so that the hybrid cell now produces large amounts of antibodies; (4) only those hybrid cells that produce antibodies against the desired antigen are isolated; (5) the isolated hybrid cells are multiplied (cloned), and the antibodies they produce are isolated.

Treatment of acquired immunodeficiency syndrome (AIDS)

Acquired immunodeficiency syndrome is caused by the human immunodeficiency virus (HIV), which exists in two main forms: HIV-1 and HIV-2. The virus damages the host's immune system, making it more susceptible to infections and malignancies. HIV is an RNA virus, with only one RNA strand. It enters CD4+ T lymphocytes and macrophages, where it multiplies, reducing the number of these cells and causing immunodeficiency. It usually takes 3 to 10 years from the moment of infection until the immunodeficiency syndrome is fully manifested. The virus multiplies by using its RNA, with the help of the enzyme reverse transcriptase, to create DNA, which enters the nucleus of the host cell, integrates into its genome, and synthesizes many copies of the viral RNA. These copies then become complete viruses, and leave the host cell, leading to its death.

Current antiviral therapy cannot cure AIDS, but it can delay the onset of the disease. That is why therapy is started as early as possible. It used to be thought that therapy should be started when the CD4 lymphocyte count was less than 350/mcl and the viral load was greater than 50,000/ml, but today the prevailing view is that antiretroviral therapy should be started as soon as it is known that a person is infected with HIV. A combination of drugs that act in different ways on the HIV virus is always used. There are currently 6 groups of anti-HIV drugs:

1. nucleoside reverse transcriptase inhibitors,
2. nucleotide reverse transcriptase inhibitors,
3. non-nucleoside reverse transcriptase inhibitors,
4. protease inhibitors,
5. virus entry inhibitors, and
6. viral integrase inhibitors.

The most commonly used combination is a combination of 2 nucleoside inhibitors with one non-nucleoside inhibitor or one protease inhibitor; such a combination is called "**highly active antiretroviral therapy**". **Nucleoside reverse transcriptase inhibitors** are phosphorylated in cells to the triphosphate form, and then, under the action of reverse transcriptase, are incorporated into the viral DNA. However, since they lack the 3' - hydroxyl group, they lead to the interruption of the growth of the viral DNA chain, preventing further replication of the virus. Since they also inhibit DNA polymerase in mitochondria, they can cause **lactic acidosis, hepatic steatosis and its enlargement**. Therefore, laboratory signs of hepatotoxicity must be monitored when using all drugs in this group. The first drug in this group was **zidovudine (azidothymidine)**, an analogue of thymidine. Zidovudine is well absorbed after oral administration, binds up to 40% to plasma proteins and is metabolized in the liver. Only 15% of the drug is excreted unchanged in the urine. In addition to AIDS therapy, zidovudine is also used for the prophylaxis of infection after exposure to infectious material, as well as for the prevention of prenatal and perinatal transmission of the virus from mother to newborn. **Bone marrow damage** occurs in about 30% of patients taking zidovudine; confusion, fatigue, myopathy or myositis occur much less frequently.

Stavudine is a nucleoside analogue of thymidine, which, in addition to AIDS therapy, is also used for the prophylaxis of infection after exposure to infectious material. It is well absorbed, not metabolized, and excreted mostly in the urine. In addition to insomnia and myalgia, stavudine can cause peripheral **neuropathy** of the sensory type. Stavudine should never be combined with didanosine (because the risk of pancreatitis increases), nor with zidovudine (because it inhibits stavudine phosphorylation, and thus its activity).

Didanosine is an adenosine analogue, which, in addition to the treatment of AIDS, is also used for the prophylaxis of infection after exposure to infectious material. The bioavailability after oral administration of this drug is about 40%; the drug is metabolized in the liver, as are other purine bases. Among the side effects, it can cause peripheral **neuropathy, pancreatitis**, bone marrow damage and eye damage (retinal depigmentation and optic neuritis). The combination of zalcitabine with didanosine should be avoided, because the risk of peripheral neuropathy increases.

Lamivudine also belongs to this group of drugs, and is described in the previous chapter. **Emtricitabine** is **a fluoro derivative of lamivudine**, the specific side effect of which is hyperpigmentation of the palms and soles. **Abacavir** is a guanosine analogue that is used in addition to AIDS therapy for the prophylaxis of infection after exposure to infectious material. It is often prepared in fixed combinations with zidovudine or lamivudine. Abacavir is extensively metabolized in the liver by alcohol dehydrogenase. About 5% of patients receiving this drug develop a potentially fatal allergic reaction, manifested by fever, rash, and respiratory symptoms. **Zalcitabine is the least effective** of all nucleoside reverse transcriptase inhibitors. It is a cytidine analogue used to treat AIDS. It is well absorbed after oral administration, is not metabolized, and is excreted unchanged by the kidneys. It causes peripheral neuropathy in more than 50% of patients. Stomatitis, esophageal ulcers, and pancreatitis may occur.

Nucleotide reverse transcriptase inhibitors have only one representative: **tenofovir disoproxil fumarate.** It is a prodrug that is converted in the body to tenofovir, a nucleoside analogue of adenosine. Tenofovir is effective in the treatment of AIDS even when resistance to nucleoside reverse transcriptase inhibitors has developed. It has a low oral bioavailability (25%), is not

metabolized, and is excreted unchanged by the kidneys. Tenofovir is well tolerated because it does not have the same mitochondrial toxicity as nucleoside inhibitors.

Non-nucleoside reverse transcriptase inhibitors do not require phosphorylation for their action. They directly inhibit the activity of viral reverse transcriptase, so they act additively with nucleoside inhibitors. Resistance to them develops rapidly, so they are never used alone, but only in combination with nucleoside reverse transcriptase inhibitors. Since they are metabolized in the liver, and in doing so induce cytochrome P450 enzymes, these drugs interact with many other drugs that use the same metabolic pathway. The absorption of non-nucleoside reverse transcriptase inhibitors and protease inhibitors is greatly affected by the acidity of the gastric juice and the time of taking the drug in relation to meals. Therefore, care should be taken when taking proton pump inhibitors or H2 blockers at the same time. In addition to the treatment of AIDS, **efavirenz** is also used for the prophylaxis of infection after exposure to infectious material. The drug can cause rash and an increase in liver enzymes and serum cholesterol levels. It has a strong effect on the **central nervous system,** causing: insomnia, euphoria, agitation, impaired thinking, nightmares and hallucinations. It is teratogenic, so patients should use contraception. Efavirenz induces CIP3A4 and inhibits CIP2C9 and CIP2C19, so it enters into numerous interactions with other drugs that are metabolized through the same enzymes. **Nevirapine** is used only for the treatment of AIDS. In the first 12 weeks of its use, special caution is required, as severe hepatitis and/or Stevens-Johnson syndrome may occur. Nevirapine induces CIP3A4. **Delavirdine** is also used only for the treatment of AIDS. The most common side effect is a rash with itching, which resolves over time. **Etravirine,** similar to efavirenz, induces CIP3A4 and inhibits CIP2C9 and CIP2C19. Sometimes etravirine causes a severe allergic reaction with rash, which can end in failure of individual organs, e.g. liver. In addition to etravirine, newer non-nucleoside reverse transcriptase inhibitors include **rilpivirine,** which is used in infections with viruses resistant to older drugs in this group.

Viral protease inhibitors are used in the treatment of AIDS, but always in combination with drugs from other groups. All cause gastrointestinal complaints and paresthesias, lead to hyperglycemia and insulin resistance, and cause hypercholesterolemia and hypertriglyceridemia. They also lead to central accumulation of adipose tissue, similar to that seen with the use of corticosteroids (buffalo hump, breast enlargement). Hepatotoxicity is also possible. Since they are metabolized in the liver by CIP3A4 and inhibit this enzyme, they interact with numerous drugs that use the same metabolic pathway.

Protease inhibitors include **saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, darunavir, and fosamprenavir. Ritonavir** is the most toxic of them all, and interacts with other drugs the most, because in addition to inhibiting CIP3A4 and CIP2D6, it induces CIP1A2. Today, it is used exclusively in conjunction with other protease inhibitors, in order to increase their serum concentration due to cytochrome inhibition. **Indinavir,** in addition to the side effects characteristic of the entire group, causes nephrolithiasis, especially in children (up to 30%); to prevent this side effect, it is necessary for children to drink at least 1.5 liters of water per day. **Nelfinavir** is the least toxic of all protease inhibitors, but can cause diarrhea. **Amprenavir** is made as an oral solution, which contains a lot of propylene glycol; therefore, it should not be given to children under 4 years of age and pregnant women (propylene glycol causes hyperosmolarity, lactic acidosis, convulsions and respiratory depression). **Fosamprenavir is a prodrug, which is converted to amprenavir.** This group of drugs also includes **saquinavir, lopinavir, darunavir and atazanavir.** The latter drug has specific side effects: it prolongs the QT interval and interferes with bilirubin excretion. **Tipranavir** is a newer protease inhibitor that is given in cases of resistance to other drugs in this group. It can cause hepatitis as a side effect.

Inhibitors of virus entry into lymphocytes

Enfuvirtide prevents HIV from entering lymphocytes by blocking the viral ***transmembrane protein gp41,*** which enables fusion of the viral membrane with the lymphocyte membrane, while ***maraviroc*** does so by blocking the chemokine CCR5 receptor on lymphocytes for viral glycoproteins**.** While enfuvirtide, as a protein drug, is administered parenterally, maraviroc is administered orally. Both drugs are used only as add-on therapy to reverse transcriptase inhibitors, in patients who have not responded well to primary therapy**.**

Inhibitors of viral integrase

Raltegravir, elvitegravir and dolutegravir are inhibitors of viral integrase, an enzyme that integrates viral DNA into the host chromosomes, thereby enabling viral replication. Raltegravir, elvitegravir and dolutegravir are administered orally. They are used in combination with other antiretroviral drugs to treat patients at all stages of the disease. Raltegravir can cause myopathy and **rhabdomyolysis**. Since they are metabolized by cytochromes, elvitegravir and dolutegravir interact with other drugs, while this

is not the case with raltegravir, which is only conjugated in the liver. Dolutegravir acts on some strains of the virus that are resistant to raltegravir and elvitegravir.

AIDS drugs and pregnancy

To prevent mother-to-child transmission of HIV, a pregnant woman should continue combination antiretroviral therapy throughout her pregnancy. Antiretroviral drugs that cross the placenta well and have fewer potential adverse effects on the mother and fetus include: **zidovudine, lamivudine, nevirapine, atazanavir, lopinavir, and ritonavir**. Treatment regimens used during pregnancy should be based on the above drugs whenever possible. Mothers with AIDS who have an HIV-negative newborn should not breastfeed, as the risk of transmission of the virus through breastfeeding is 10-20%.

MEDICINES AGAINST THE FLU VIRUS

Drugs that act on influenza viruses are used only in patients who are at particular risk (chronic respiratory disease, significant cardiovascular disease, chronic kidney disease, immunosuppression, diabetes and age over 65 years).

Once widely used, amantadine is increasingly avoided. Today, **zanamivir or oseltamivir** are used in adults, and only oseltamivir in children. The condition is that therapy is started within 48 hours of the onset of symptoms.

There are three types of influenza viruses: A, B and C. Only types A and B cause significant disease in humans. The best way to prevent influenza is to use a vaccine, which is given to people at particular risk (see above).

Amantadine is a synthetic tricyclic amine, and **rimantadine** is its alpha-methyl derivative. Both drugs inhibit the M2 ion channel in the membrane of influenza type A virus; they have little effect on type B. M2 is a hydrogen ion channel that, when blocked, prevents the "undressing" of viral RNA. If these drugs are administered within 48 hours of the onset of symptoms, the duration of fever and malaise is shortened by 1–2 days, and viral shedding is reduced. There is no evidence that these drugs prevent complications. Amantadine and rimantadine can also prevent influenza A infection in 70–90% of patients.

Amantadine is rapidly and completely absorbed, and penetrates well into all tissues. It is excreted unchanged by glomerular filtration and tubular secretion. Rimantadine is also well absorbed, but it is hydroxylated or conjugated in the liver, so that only 25% of the drug is excreted unchanged in the urine.

Amantadine is a more toxic drug than rimantadine. **Amantadine causes depression, confusion, anxiety, and psychomotor incoordination.** High doses cause delirium, hallucinations, and suicidal tendencies. Cardiovascular toxicity is also manifested: arrhythmias, heart failure. It also exhibits antimuscarinic effects: urinary retention and dry mouth. Both amantadine and rimantadine can cause **convulsions**. Amantadine is teratogenic, and rimantadine is embryotoxic.

Zanamivir is an inhibitor of viral neuraminidase. Neuraminidase and hemagglutinin are found on the surface of the influenza virus. Hemagglutinin binds to receptors on the host cell that contain neuraminic acid, which allows the virus to enter the cell. Neuraminidase degrades the receptors for hemagglutinin, and allows the release of progeny viruses from the host cell. Neuraminidase inhibitors prevent the release of progeny viruses, thereby preventing the spread of the virus.

Zanamivir is administered by inhalation. Of the administered dose, about 15% is absorbed into the blood and then excreted unchanged by the kidneys. Zanamivir is used for the treatment (shortens the duration of the disease by 1 day) and prophylaxis of influenza A and B infections, but only in patients older than 7 years. It can cause bronchospasm and allergic reactions, so it is contraindicated in patients with asthma or severe chronic obstructive pulmonary disease.

Similar to zanamivir is **laninamivir**, which inhibits neuraminidase and is administered **by inhalation**; for now, it is only used in Japan.

Oseltamivir is also an inhibitor of influenza virus neuraminidase. It is administered orally, is well absorbed, and is then converted in the liver to the active form oseltamivir carboxylate. The unchanged drug and the active metabolite are excreted by the kidneys. It works well against influenza A and B; it is used in treatment in children older than one year and adults, and in prevention it is used only in people older than 13 years. It reduces the duration of symptoms by half a day, and shortens absence from work by two full days; it also reduces the incidence of complications. It can prevent influenza virus infection in 90% of exposed individuals.

Oseltamivir is well tolerated: nausea and vomiting occur in 3-7% of patients, and bronchitis, insomnia, and liver cell damage are rare.

Peramivir is another new neuraminidase inhibitor, which is administered intravenously, and once. It does not differ significantly from oseltamivir in terms of efficacy, but causes moderate or severe neutropenia in about 8% of patients.

DRUGS AGAINST VIRAL HEPATITIS

There are five viruses that cause hepatitis: A, B, C, D and E. Hepatitis A and E are fecal-oral infections that do not tend to become chronic. After the acute phase, the patient is definitively cured. Hepatitis B and C pose the greatest problem, because after the acute infection they become chronic; the hepatitis D virus is only a companion of the B virus, and cannot cause infection on its own.

Hepatitis B is a DNA virus that multiplies in hepatocytes. First-line therapy for hepatitis B consists of **pegylated interferon alpha, entecavir and tenofovir disoproxil fumarate**. Pegylated interferon alpha is a conjugate of interferon alpha and monomethoxy polyethylene glycol. Thus, **"pegylated" interferon alpha** is actually a depot preparation, which can be administered once a week, subcutaneously (otherwise, regular interferon was administered three times a week), and allows for higher and more stable concentrations of interferon alpha to be achieved in the blood. **Entecavir** is a guanosine analogue that interferes with the functioning of viral DNA polymerase. **Tenofovir** disoproxil fumarate is a nucleotide analogue of adenosine monophosphate that inhibits reverse transcriptase (already mentioned in the chapter on the treatment of AIDS) and hepatitis B virus DNA polymerase. **Telbivudine** is a thymidine analogue, which, after phosphorylation, is incorporated into the DNA of the hepatitis B virus. It has a hepatotoxic effect and damages striated muscles. These drugs are used as monotherapy at the beginning of treatment, and can later be combined with each other, if the patient has not responded adequately to monotherapy. Treatment of chronic hepatitis B lasts at least a year.

Second-line drugs, **lamivudine and adefovir** (an acyclic analogue of adenosine monophosphate, which inhibits viral DNA polymerase), can also be used in the treatment of hepatitis B. Side effects of adefovir include: impaired kidney function, asthenia, and worsening of hepatitis after discontinuation of the drug. Lamivudine and adefovir are used less frequently today, because their efficacy is significantly lower than first-line drugs, and because viral resistance to them is more common and faster.

Hepatitis C requires treatment if patients are positive for hepatitis C viral RNA. Just a few years ago, the mainstay of chronic hepatitis C therapy was pegylated interferon alpha and ribavirin. Oral therapy for chronic hepatitis C is now available, which is highly effective and can completely cure almost all patients in just 12 weeks.

In Australia, a national program is active to eradicate the hepatitis C virus in the human population using these new drugs; general practitioners are authorized to prescribe these drugs without consulting a specialist.

The key point in the treatment of hepatitis C is to determine the genotype of the virus and the concentration of viral particles, because the choice of drug and prognosis depend on this. Combinations of drugs are always used, and fixed ones. The following combinations of drugs are present in practice:

1. **Sofosbuvir + velpatasvir** is a combination that is administered for 12 weeks, and acts on all 6 genotypes of the hepatitis C virus. Sofosbuvir inhibits NS5B RNA polymerase, and velpatasvir NS5A, i.e. nonstructural protein 5A, which plays an important role in the assembly of the viral particle and its exit from the cell. Sofosbuvir interacts with amiodarone, causing symptomatic bradycardia, as well as with other drugs that induce cytochromes.

2. The combination of **sofosbuvir + daclatasvir** is not fixed, it is used for 12 weeks. In this combination, sofosbuvir acts only on genotypes 1a and 1b, and daclatasvir on all genotypes. Daclatasvir inhibits NS5A, i.e. nonstructural protein 5A, which is important for the assembly of the viral particle and its exit from the cell. If the patient is simultaneously receiving statins, their doses must be reduced due to daclatasvir.

3. **Sofosbuvir + ledipasvir**, a fixed combination, is used for 8-12 weeks, and is effective against genotypes 1, 4 and 6 of the hepatitis C virus (sofosbuvir only affects genotypes 1a and 1b, and ledipasvir on 1, 4 and 6). Sofosbuvir inhibits NS5B RNA polymerase, and ledipasvir inhibits NS5A, i.e. non-structural protein 5A. Proton pump inhibitors reduce the absorption of ledipasvir, which should be taken into account in practice.

4. **Paritaprevir/ritonavir/ombitasvir** fixed combination + **dasabuvir** is effective only against genotype 1, and is used for 12 weeks. Paritaprevir – inhibits NS3/4A protease important in post-translational modification of proteins; ritonavir – increases the concentration of paritaprevir by inhibiting its metabolism on cytochromes; ombitasvir – inhibits NS5A; and dasabuvir – inhibits NS5B RNA polymerase. The dose of some statins should be reduced in patients receiving this combination.

5. **Elbasvir + grazoprevir**, a fixed combination, which acts on genotypes 1 and 4, and is administered for 12 weeks. Elbasvir inhibits NS5A, i.e. nonstructural protein 5A that plays an important role in the assembly of the viral particle and its exit from the cell, and grazoprevir inhibits NS3/4A protease important in post-translational modification of proteins. These drugs also interact with cytochrome inducers.

ANTIMALARIAL MEDICATION

Malaria is caused by intracellular protozoa from the Plasmodium group. The mosquito feeds on the blood of a malaria patient and ingests **Plasmodium gametocytes** (male and female). The gametocytes fuse in the mosquito's stomach to form a zygote. The zygote penetrates the stomach wall and transforms into an oocyst, which, upon maturation, releases a large number of **sporozoites**. The sporozoites enter the mosquito's bloodstream and its salivary glands. When the mosquito bites a healthy person, the sporozoites are injected into the blood. They travel through the blood to the liver cells, where they enter and multiply (this is the so-called exoerythrocytic phase of development). The exoerythrocytic phase ends with the shedding of infested liver cells and the released **merozoites** now enter the erythrocytes. The species **Plasmodium falciparum and Plasmodium malariae** completely leave the liver, while **Plasmodium ovale and Plasmodium vivax** remain partly in the liver cells in the form of **hypnozoites**, which can later be reactivated and lead to a relapse of the disease. Merozoites grow in erythrocytes (feeding on hemoglobin) and multiply, creating conglomerates called **schizonts**. When they grow sufficiently, they lead to the rupture of erythrocytes and the release into the blood of a large number of new merozoites that enter new erythrocytes. In addition to merozoites, **the schizonts also partly form gametocytes** that can infect “healthy” mosquitoes, thus closing the cycle.

Since the rupture of erythrocytes and the release of merozoites occur synchronously (at once), the clinical picture of malaria develops in attacks. In Plasmodium falciparum, attacks occur every 48 hours, in Plasmodium vivax and Plasmodium ovale every 72 hours, and in Plasmodium malariae every 96 hours.

Drugs to terminate malarial attacks act on schizonts in erythrocytes by **interfering with the utilization of hemoglobin**. The drug of choice is still **chloroquine**, except in regions where chloroquine-resistant falciparum malaria dominates. Plasmodium feeds on hemoglobin, with heme appearing as a waste product. Heme is toxic to the parasite, so in order to protect itself, it polymerizes heme into the pigment hemozoin. **Chloroquine interferes with the formation of hemozoin**. Other quinolines are used for resistant forms: **quinine** (a natural alkaloid from the bark of the cinchona tree) and **mefloquine**. All aminoquinolines act only on the erythrocyte forms of malaria - schizonts. Their side effects are similar: they affect excitable tissues, the CNS (ringing in the ears, visual disturbances, confusion, "quinine intoxication", headache) and the heart (prolongation of the QRS complex, arrhythmias). In addition, in people with a deficiency of the enzyme glucose-6-phosphate dehydrogenase, they can increase hemolysis. They are administered orally, and quinine is also administered parenterally. Quinine and mefloquine are not used in pregnancy because they are teratogenic.

All aminoquinolines (chloroquine, amodiaquine, mefloquine) can also be used for malaria prophylaxis during a stay in a malarious region. In this case, they do not actually prevent malaria infestation, but rather prevent malaria attacks after infestation has occurred.

For resistant forms of malaria, drugs that interfere with the synthesis of folic acid in the parasite can also be used. These are pyrimethamine and proguanil. **Pyrimethamine** is often **combined with sulfonamides** or sulfones (which interfere with the synthesis of dihydrofolic acid), thus achieving the so-called "sequential block": sulfonamides block the first step in the synthesis of tetrahydrofolic acid, and pyrimethamine the second (blocks the transition of dihydrofolic acid to tetrahydrofolic acid). In addition to acting on schizonts, **proguanil also acts to some extent on hepatic forms of the parasite**. These drugs are well tolerated and can be used in pregnancy, as well as for the prevention of malaria. The atovaquone/proguanil combination is used for the treatment of Pl. falciparum that is resistant to chloroquine. It can also be used for prevention. **Atovaquone inhibits electron transport**, the synthesis of ATP and pyrimidine bases. Proguanil gives the active metabolite cycloguanil, which inhibits dihydrofolate reductase.

Primaquine (8-aminoquinoline) acts only on the hepatic forms of the malaria parasite and **on gametocytes** in the blood. Therefore, it is used in conjunction with drugs that interrupt the malaria attack to eradicate malaria in patients infested with Plasmodium ovale and Plasmodium vivax. Primaquine is transformed in the liver to an active metabolite. Its side effects are similar to those of 4-aminoquinoline: headache, itching, gastrointestinal disorders and hemolytic anemia in people with glucose-6-phosphate dehydrogenase deficiency. Primaquine is administered for a total of 14 days; a new drug that acts on the hepatic forms of the parasite and on gametocytes has recently been used – **tafenoquine**. The efficacy and safety of tafenoquine are almost the same as that of primaquine, but it has one important advantage – it is administered in only one dose.

In recent years, due to the increasing occurrence of multidrug-resistant strains of the malaria parasite, an old Chinese medicine made from the QING-HAO plant and known as **qinghaosu** has been introduced into practice. It contains the lactone **artemisinin** with endoperoxide, which is effective against erythrocytic forms of malaria. The heme and divalent iron ingested by the parasite catalyze the opening of the peroxide bridge in the artemisinin molecule; the consequence of this reaction is the

formation of free radicals, which lead to the death of the parasite. So far, no resistance of malarial parasites to the aforementioned drug has been observed.

Artemisinin can only be administered orally, because it is insoluble. The absorption of artemisinin is incomplete (bioavailability 43%). Artemisinin derivatives that can be administered intramuscularly have been synthesized: **artemether, artesunate and arteether**. Both artemisinin and its derivatives are metabolized in the liver, via cytochrome CIP3A4. Most of these drugs have a short half-life (several hours), except for arteether (the half-life is about 24 hours).

Side effects of artemisinin and its derivatives are rare, so it can be said that they are very well tolerated. However, after prolonged use, drug accumulation and **neurotoxicity** occur. Therefore, artemisinin and its derivatives are not used in prophylaxis, but only in the treatment of malaria.

Another drug is used alternatively in the treatment of malaria: **halofantrine**. It acts only on the erythrocytic form of the parasite. Resistance rarely occurs. It is used orally, only if other antimalarials do not work. It is transformed in the liver to an active metabolite. The half-life of halofantrine is two days, and the half-life of its metabolite is 3-5 days.

Table 34. Doses of antimalarials.

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL	INDICATION
Chloroquine	Oral	600 mg	After 8 h 300 mg more, then 300 mg/24 h during 2 days	Stopping an attack
	Oral	300 mg	7 дана	Prophylaxis
Primaquine	Oral	15 mg	24 часа (током 15 дана)	Eradication of Plasmodium vivax and ovale
Quinine	Oral	600 mg	8 часова (током 7 дана)	Treatment of falciparum malaria

Halofantrine causes itching and skin rash. It prolongs the QT interval in the heart, which can lead to ventricular arrhythmias. A drug very similar to halofantrine has been synthesized, which does not prolong the QT interval. Its name **is lumefantrine**; it is not used alone, but in combination with artemether.

AMEBICIDES

Amoebas are protozoa (Entamoeba histolytica) that parasitize the small and large intestines of humans. They exist in a cystic, non-invasive form that is found in the intestinal lumen and in a vegetative form (trophozoites) that penetrates the intestinal wall and further, through the blood to the liver.

Metronidazole (nitro-imidazole) is the most effective against vegetative forms of amoebas, which has a cytotoxic effect in anaerobic conditions of amoeba organelles. Anaerobic microorganisms possess the enzyme pyruvate-ferredoxin oxidoreductase, which reduces metronidazole; the reduced drug interferes with the transcription process in the parasite. In addition to amoebas, metronidazole is effective against **giardiasis, trichomoniasis, blastocyst infestation, Balantidium coli, anaerobic bacteria and a parasite from the group of worms, Dracunculus medinensis**.

Metronidazole can be administered both orally and parenterally, for at least 15 days. It penetrates all tissues (including the CNS) well. Less than 20% of the drug binds to plasma proteins. It is metabolized in the liver, and the unchanged drug and metabolites are excreted in the urine. Metronidazole has a good effect on both amoebae in the intestinal wall and amoebae in liver abscesses, but it has no effect at all on cystic forms in the intestinal lumen! Therefore, it must be administered together with a luminal amebicide.

Metronidazole causes a metallic taste in the mouth, headache, turns urine **dark** and can cause peripheral neuropathy after prolonged use. It also interferes with alcohol metabolism (blocks aldehyde dehydrogenase), so drinking alcohol during metronidazole therapy is accompanied by the accumulation of acetaldehyde (flushing of the face, nausea, vomiting).

Another nitroimidazole that can be used in the treatment of invasive forms of amebiasis is tinidazole**. Tinidazole** interferes with the synthesis of DNA of parasites and breaks DNA chains. In addition to amoebae, it is effective against Giardia lamblia and Trichomonas vaginalis, Helicobacter pylori, Gardnerella vaginalis and many anaerobic bacteria. It is administered orally and is well tolerated: the most common side effects are transient leukopenia and dark urine.

Diloxanide-furoate is effective against cystic forms of amoebae in the intestinal lumen. In the intestinal lumen, this drug is chemically broken down into furoate and diloxanide, which destroys the amoeba cysts. It is well tolerated - the only side effect is flatulence. It is absorbed into the bloodstream, metabolized in the liver, and excreted in the urine as a glucuronide.

Previously, **iodoquinol and clioquinol** were used to treat amebiasis, but they were shown to have a pronounced toxicity: iodoquinol caused an enlargement of the thyroid gland, and clioquinol caused subacute myelo-optic neuropathy accompanied by loss of vision.

Sometimes amoebic liver abscesses do not respond to the use of metronidazole. In this case, drugs are given that concentrate in the abscess and have an amebicidal effect. These are the **antimalarial chloroquine and the ipecacuanha alkaloid emetine** in the form of dehydroemetine. The use of emetine should be carried out only in hospital conditions due to its pronounced cardiotoxicity.

Some antibiotics also have an amebicidal effect. Tetracyclines lead to a decrease in the number of bacteria in the intestinal lumen, which amoebas normally feed on. The aminoglycoside **paromomycin** has direct amebicidal activity when administered orally. Antibiotics are used in the treatment of amebiasis only if other amebicides cannot be used (for example, due to allergy).

Table 35. Doses of the most commonly used amebicides.

DRUG	INDICATION	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Metronidazole	Amoebic abscess and vegetative forms in intestines	Oral	750 mg	8 h
Diloxanid-furoate	Cysic forms in intestines	Oral	500 mg	8 h
Chloroquine	Amoebic abscess	Oral	500 mg	24 h

TRICHOMONIASIS

Trichomoniasis is a very common genital infection caused by the protozoan Trichomonas vaginalis. It responds well to a seven-day course of metronidazole (250 mg/8 hours, orally) or to a single dose of tinidazole of 2 grams. Both sexual partners should always be treated at the same time, even if one of them may not have symptoms!

GIARDIA LAMBLIA

Giardia lamblia is a protozoan that inhabits the duodenum and causes dyspeptic symptoms. It is sensitive to metronidazole, which should be administered for 7 days (250 mg/8 hours, orally), and to tinidazole, which is administered in a single oral dose of 2 grams. Therapy is usually repeated after 4-6 weeks.

Nitazoxanide is a synthetic drug that has a beneficial effect on diarrhea caused by Cryptosporidium parvum or Giardia lamblia. It is used in children, in the form of an oral preparation, which is administered for 3 days. C. parvum and G. lamblia are found in well water and swimming pools, from where they reach the digestive tract of children. In children, they cause chronic diarrhea that can slow growth, cause malnutrition, and even lead to death. Nitazoxanide is currently the only drug that acts on C. parvum, fortunately with great efficacy.

The side effects of this drug are mild and transient, mainly affecting the digestive tract: vomiting, abdominal pain and diarrhea.

LEISHMANIASIS AND TRYPANOSOMIASIS

Leishmaniasis is an infection with protozoa of the genus Leishmania. The reservoir of infection are dogs and rodents, from which leishmania is transmitted to humans by tiny mosquitoes of the genus Phlebotomus. There are two forms of the disease: cutaneous and visceral. The cutaneous form is manifested by the formation of ulcers, and the visceral (called "kala-azar") by an enlargement of the liver and spleen with an inflammatory syndrome.

Trypanosomiasis is caused by the protozoa Trypanosoma. In Africa, this disease is transmitted by "**tsetse**" flies, and in South America by **bedbugs**. The African form of the disease has two phases: in the first, hemolymphatic phase, the disease resembles other systemic infectious diseases, and in the second phase, the brain is affected, with drowsiness and mental decline (the so-called "**sleeping sickness**"). The South American form of the disease is characterized by lymphadenopathy and a prolonged febrile state (**Chagas disease**).

Organic compounds of **pentavalent antimony** are used for the treatment of leishmaniasis: **sodium stibogluconate and meglumine antimonate**. They bind to the sulfhydryl groups of the parasite's macromolecules, interfering with their function.

Antimony compounds are administered only parenterally due to their irritating effect on the gastric and intestinal mucosa. They are not metabolized in the body, but are excreted unchanged in the urine (the half-life is about 24 hours).

Sodium stibogluconate and meglumine antimonate are used for the treatment of both visceral and cutaneous leishmaniasis. For the treatment of the **visceral form of the disease, the antifungal drug amphotericin B (liposomal preparation) is used** as the drug of first choice, which is less toxic than antimony compounds. Instead of amphotericin B, **pentamidine** can be administered intramuscularly. Pentamidine interferes with the functioning of DNA, RNA and protein synthesis of the parasite. The toxicity of pentamidine is reflected in damage to the renal tubules, liver cells and cytopenia in the peripheral blood. A new drug for visceral leishmaniasis that is effective, inexpensive and has few side effects is **miltefosine.** Miltefosine is an analogue of phosphocholine that interferes with the functioning of the parasite membrane and the transmission of signals across it. Cure with the help of oral administration of miltefosine for 4-6 weeks is achieved in 97% of patients. Adverse effects include gastrointestinal upset and transient elevations in serum creatinine.

Adverse effects of antimony compounds include pruritic rash, pancreatitis, liver damage, and anaphylactoid reactions.

Pentamidine and suramin are used first-line for the treatment of trypanosomiasis, followed by **arsenic compounds, eflornithine, nifurtimox, and benznidazole**.

Pentamidine is used to treat infection with Trypanosoma brucei gambiense, and suramin is used to treat infection with Trypanosoma brucei rhodesiense.

Suramin kills trypanosomes by a mechanism that is still poorly understood. It cannot be absorbed from the gastrointestinal tract, so it is administered only intravenously. It binds very tightly to plasma proteins, and therefore remains in the blood for months. It does not penetrate the central nervous system. It is not metabolized, but is excreted very slowly in the urine. It accumulates in reticuloendothelial cells.

Suramin is active only against African trypanosomes, while it has no effect on South American ones. In advanced disease, it is always used in combination with arsenic compounds.

In susceptible individuals, intravenous administration of suramin is accompanied by nausea, hypotension, and loss of consciousness. After prolonged administration, it can cause peripheral neuropathy and albuminuria.

Eflornithine inhibits the enzyme ornithine decarboxylase, which disrupts the synthesis of polyamines in parasites. Like suramin, eflornithine is administered intravenously. It does not bind to plasma proteins, so it is rapidly excreted in the urine as unchanged drug (the half-life is only 3 hours). **It penetrates well into the central nervous system. It is used to treat the African form of trypanosomiasis, and only Trypanosoma brucei gambiense**. The most common side effects are anemia and leukopenia.

The arsenic compounds used to treat trypanosomiasis are **melarsoprol and triparsamide**. Arsenic from these molecules binds to the sulfhydryl groups of the parasite's enzymes, inactivating them. Arsenic compounds are administered intravenously. Since they penetrate well into the central nervous system, they are used to treat the cerebral form of African trypanosomiasis. They are eliminated quickly.

The most significant side effects of arsenic compounds are **abdominal pain, encephalopathy, proteinuria, peripheral neuropathy**, and rash. Melarsoprol is less toxic than triparsamide.

Nifurtimox is a substance that, after its reduction, leads to the formation of free radicals. Since trypanosomes do not have enough enzymes to defend against free radicals (there is no catalase), lipid peroxidation occurs and the parasite dies. The drug is well absorbed after oral administration. It is rapidly metabolized; its metabolites are excreted in the urine.

Nifurtimox is used primarily for the treatment of South American trypanosomiasis, but it can also be used for African forms of this disease. Treatment lasts several months. The drug is well tolerated: in a small number of patients it causes **insomnia, convulsions and myalgia**.

Benznidazole is another effective drug for South American trypanosomiasis, which is administered orally for two months. It creates free radicals and electrophilic metabolites which then bind to the macromolecules of the parasite and block their functions. It causes skin rash, peripheral polyneuritis and leukopenia.

TREATMENT OF SCABIES

Scabies is caused by the insect Sarcoptes scabiei, which parasitizes the skin, causing unbearable itching. Scabies is treated by applying a 25% **benzyl benzoate** preparation to the skin for 3 consecutive days. Benzyl benzoate is not toxic. It should be applied to the entire body except the neck and head (because the parasite does not settle in these areas). In addition to benzyl benzoate, **0.3% lindane**, an organochlorine insecticide, can be used. After application, it is left on the skin for 10 hours, then washed off. Its use is more dangerous, because if applied excessively, it can be absorbed through the skin and cause convulsions.

In the absence of other drugs, a traditional drug is used: 5% elemental **sulfur ointment**. This drug, however, must be applied much longer than the new drugs: it must be applied to the skin for 8 consecutive days. Since it is completely non-toxic, it can be used in pregnant women and infants.

Don't forget: if scabies occurs, always treat all family members at the same time!

HEAD LICE TREATMENT

Head lice (Pediculus capitis) and pubic lice (Phthirius pubis) are treated by applying special shampoos to the infested areas for 10 minutes and then rinsing. These shampoos contain either **1% lindane** or the plant-based insecticides **pyrethrins and permethrin.** Lindane is more toxic and less effective than plant-based insecticides, which cause only mild skin irritation. After shampooing and rinsing, the hair should be carefully combed with a wide-toothed comb dipped in a **10% acetic acid solution** (to remove nits, i.e. lice eggs and larvae).

Body lice (Pediculus corporis) are treated by exposing clothing to hot steam in an autoclave (or, in wartime conditions, in a "Serbian barrel") and by spraying the clothing with the organochlorine insecticide DDT.

TREATMENT OF HELMINTHIASIS

Helminths can parasitize in humans in the intestinal lumen or in tissues. Roundworms (nematodes) and tapeworms (cestodes) parasitize in the intestinal lumen, and threadworms (filariae) and flukes (trematodes) parasitize in tissues. In our country, the most common nematodes are the small (Enterobius vermicularis) and large (Ascaris lumbricoides) white worms. Trichuris trichiura, Strongyloides stercoralis and Ankylostoma duodenale are much less common. Enterobius and ascaris can be successfully treated with **mebendazole**, a benzimidazole preparation that inhibits **microtubule synthesis** and thus interferes with glucose uptake by parasites (Enterobius 100 mg in a single dose, Ascaris 100 mg every 12 hours for three days). Mebendazole is very poorly absorbed (only 10% of the dose taken) so side effects are rare (abdominal pain, diarrhea). Mebendazole can also be used to treat hookworm and whipworm infestations.

Thiabendazole and albendazole are in the same group of benzimidazoles. Their mechanism of action is the same as mebendazole; thiabendazole additionally inhibits the enzyme fumarate reductase, which is necessary for the formation of adenosine triphosphate (ATP). Thiabendazole is well absorbed from the digestive tract, while albendazole is poorly and variably absorbed (absorption of albendazole can be significantly increased if it is taken with a fatty meal). Both drugs are metabolized in the liver, and the metabolites are excreted in the urine.

Thiabendazole (25 mg/kg every 12 hours for 2 days) is effective against enterobius and ascaris, trichiura, trichinella, strongyloides and hookworm, so it can be used to eliminate the aforementioned nematodes. Today, thiabendazole is the drug of choice only for **strongyloides and trichinellosis**, because there are less toxic drugs for other infestations.

Albendazole has the broadest spectrum of action. In addition to the nematodes that thiabendazole is effective against, albendazole is also effective against **echinococcus cysts and cysticercosis** (a complication of taeniasis). Today, albendazole is the drug of choice for echinococcosis (800 mg/day for 28 days) and neurocysticercosis (15 mg/kg/day for 8 days). Also, some species of flukes (Opisthorchis sinensis, Clonorchis sinensis, Opistorchis viverrini) respond well to albendazole.

Trichinosis (a nematode, Trichinella spiralis, which lives briefly in the intestinal lumen and whose larvae penetrate the intestinal wall and settle in the striated muscles) is primarily treated with **thiabendazole** (25 mg/kg every 12 hours, for 3 days).

Side effects of thiabendazole include neurotoxic effects (headache, drowsiness, confusion, hallucinations, tinnitus, paresthesia, visual disturbances), hepatitis, hyperglycemia, lymphadenopathy, muscle pain, and alopecia. Albendazole has fewer side effects, and mebendazole is well tolerated, due to its low absorption.

Piperazine causes the **opening of chloride channels** in the membranes of nematode cells, their hyperpolarization and paralysis. The worms are then eliminated by intestinal peristalsis. Piperazine can be used to treat **ascariasis and enterobiasis**. It is administered orally and is well absorbed. The drug is excreted in the urine. Side effects of piperazine include gastrointestinal complaints, ataxia, visual disturbances, hypotonia, and even epileptic seizures.

Pyrantel pamoate is an agonist of nicotinic receptors, which leads to depolarization and spastic paralysis of nematodes. Paralyzed worms are expelled by intestinal peristalsis. After oral administration, most of the drug is not absorbed. Pyrantel pamoate can be used to treat **ascariasis, enterobiasis, and hookworm**. The drug is well tolerated, and only in a very small number of patients does it cause dizziness and drowsiness.

Tapeworms (tapeworms, cestodes, flukes) are best treated with **praziquantel**. In addition to cestodes, praziquantel is also effective in **schistosomiasis**. It **increases the permeability of the worm's shell to calcium**, so that its muscles first contract and then paralyze. This is followed by disintegration of the shell and death of the worm. For tapeworms, a single dose of praziquantel (10 mg/kg) is administered; in the case of Tenia solium, in order to prevent cysticercosis, two hours after the administration of praziquantel, the patient should take a laxative (15g $MgSO_4$) and expel the tapeworm from the digestive tract. For schistosomiasis, the dose is 20 mg/kg every 6 hours for a total of 3 doses.

Praziquantel is well absorbed and penetrates all tissues (the concentration in the cerebrospinal fluid is 20% of the serum concentration). It is metabolized in the liver, and the unchanged drug and its metabolites are excreted in the urine (the half-life is only about 1 hour). Its side effects are: headache, drowsiness, instability (neurological effects), mild hepatitis and musculoskeletal pain. **Niclosamide** was once used to treat tapeworms. However, since it caused vomiting more often than praziquantel, it also led to the regurgitation of pork tapeworm segments into the stomach and the development of cysticercosis. Therefore, praziquantel has completely replaced it today. Niclosamide inhibits the creation of ATP in the processes of anaerobic metabolism. By acting in this way, niclosamide causes the head of the tapeworm (scolex) to detach from the intestinal wall, so intestinal peristalsis expels the entire tapeworm. It does not destroy the tapeworm eggs. Niclozamide is not absorbed from the gastrointestinal tract, so its side effects are mild (nausea, diarrhea).

Liver fluke (Fasciola hepatica) is treated with bithionol (50 mg/kg/day orally for 5 days). The mechanism of action is related to the inhibition of the enzyme **fumarate reductase**, and thus to the reduction of ATP production in parasite cells. The drug is administered orally and is eliminated in the urine. It can cause diarrhea, nausea, vomiting, headache. Rarely, it leads to tinnitus, insomnia and fever.

Filariasis (Filaria Loa Loa, Brygia malayi, Wuchereria ban-crofti) is treated with **diethylcarbamazine**. This drug **changes the surface of microfilariae** and makes them susceptible to the action of the host's immune system. It gradually kills adult worms. It also interferes with the production of prostaglandins, which leads to vasoconstriction and difficulty in spreading microfilariae. It penetrates all tissues. Both the unchanged drug and its metabolites are excreted in the urine. Due to the sudden death of microfilariae, the so-called **Masotti reaction occurs**: fever, weakness, drowsiness, headache, cough, chest and muscle pain. The drug itself causes mild headache, weakness, nausea and vomiting. A special type of filariasis, whose microfilariae go to the eye, **onchocerciasis** (Onchocerca volvulus), is treated with another drug, **ivermectin**. Ivermectin **opens chloride channels** in the microfilariae cells, which leads to membrane hyperpolarization and paralysis. This allows the immune system to remove the microfilariae. Due to its gradual action on microfilariae, ivermectin does not cause visual impairment because the inflammatory reaction around the microfilariae in the eye is mild. That is why it is used to treat onchocerciasis, and not diethylcarbamazine. Ivermectin can also cause a Mazotti-like reaction due to the sudden death of a large number of microfilariae.

Ivermectin is administered orally or subcutaneously. After absorption, most of the drug is eliminated via the bile. The half-life is 12 hours.

Side effects of ivermectin are mild: itching, fever, and lymph node tenderness.

ANTISEPTICS AND DISINFECTANTS

Disinfection is the process of destroying vegetative forms of microorganisms, while leaving spores undamaged. If disinfection is carried out on human skin and mucous membranes, such a procedure is called antisepsis.

Antiseptics and disinfectants are substances that act non-specifically on microorganisms by denaturing their structural and functional proteins. They are too toxic to tissues to be applied systemically, so they are used exclusively locally. According to their chemical composition, they can be classified into 10 groups:

I) **Alcohols**. The most commonly used is ethanol (CH_3-CH_2OH) at a concentration of 70%. It is used to clean the skin before injections and before surgical interventions (then the skin is first cleaned with gasoline, then alcohol and finally with iodine).

II) **Acids**. Boric acid (H_3BO_3) is used as a 3% solution for rinsing hollow organs (bladder, vagina, rectum). In powder form, it is used to sprinkle gauze on wounds infected with Pseudomonas aeruginosa.

III) **Phenols**. The first phenol to be used was ordinary phenol, known as carbolic acid (C_6H_5OH). The English surgeon Lister was the first to start the era of antiseptics (in 1864) precisely with the use of carbolic acid. A solution of carbolic acid (3-5%) is used to disinfect instruments that cannot be sterilized by heat and to disinfect floors and walls. **Cresols** (methyl phenols) have a similar use.

IV) **Oxidizing agents**. These substances oxidize the proteins of microorganisms and thus denature them. **Potassium permanganate** ("hypermanganese", $KMnO_4$) is used in a 1:5000 dilution for washing wounds. **Hydrogen peroxide** ("hydrogen", H_2O_2) is used in a 3% solution for washing wounds; it not only oxidizes microorganisms, but also creates a foam (due to the release of oxygen) that mechanically expels impurities from the wound. It also has a local hemostatic effect. Very deep wounds

should not be washed with hydrogen peroxide because the released oxygen can enter open blood vessels and cause gas embolism. In a tenfold higher dilution (0.3%), hydrogen peroxide can be used for washing the oral cavity and oropharynx.
The compound of acetic acid with hydrogen peroxide (peracetic acid, CH3-COOOH) is used for disinfecting objects.
V) **Halogen compounds**. These are substances that have a halogen element (usually iodine or chlorine) in their molecule. Alcoholic iodine solution (iodine tincture: 6.5g iodine + 2.5g potassium iodide + 91g concentrated alcohol) is used to clean the skin before surgical intervention, to coat the wound area and to quickly prepare the surgeon's hands. More recently, iodine compounds with polyvinylpyrrolidone, so-called **povidone-iodine**, solution and foam, have been used to clean the skin. Caution should be exercised with iodine preparations in young children because excessive absorption from the skin can lead to hypothyroidism. **Carrel-Dakin** solution (sodium hypochlorite solution, NaOCl) is used to rinse wounds. A similar function is performed by a chloramine solution (p-toluenesulfane chloramide sodium, 0.25-0.5%), which can also be used to disinfect objects and floors (1-5%).
VI) **Detergents**. Detergents are surface-active substances whose cationic part penetrates the membrane of microorganisms and destroys them. The cationic part almost always contains quaternary nitrogen. **Benzalkonium chloride** is primarily used to disinfect objects and floors. **Octenidine** dihydrochloride is used to disinfect the skin before surgical and endoscopic procedures, as well as for washing wounds in very low concentrations. **Polyhexanide** is used to treat second-degree burns and bacterial vaginosis.
VII) **Soaps.** The mechanism of action of soap is the same as that of detergents, but here the part of the molecule that penetrates the membrane of microorganisms is an anion. Soaps are actually sodium or potassium salts of fatty acids. They are used to wash and disinfect the skin before surgical intervention.
VIII) **Heavy metals**. **Silver nitrate** (AgNO3) at a concentration of 0.1% (Crede's drops) has been used successfully to prevent eye infection with the causative agent of gonorrhea; one drop of this solution was instilled into each newborn's eye. Silver nitrate sticks are used as a caustic agent to remove hypertrophic granulations in wounds. Silver prepared in the form of nanoparticles ("nano silver") is also used in high dilutions for wound dressings.
Sublimate (mercuric chloride, HgCl2) is used in a dilution of 1:1000 for disinfecting objects and, in the absence of better means, for rapid disinfection of surgeons' hands after washing. The mercury compound **thimerosal** (0.001-0.004%) is used as a preservative for vaccines and serums.
IX) **Dyes**. **Gentian violet** is a natural dye that is used as a 1% solution for the treatment of resistant oral candidiasis in newborns (thrush). Rivanol is an acridine dye that is used as a 0.1% solution for wound irrigation.
X) **Aldehydes**. Formaldehyde and glutaraldehyde are used to disinfect rubber catheters and optical instruments. Instruments and catheters are placed in a closed space together with formaldehyde tablets from which the active substance slowly evaporates. Glutaraldehyde is used as a solution (2%) which must be alkalinized (pH around 8) to activate it.

IMMUNOMODULATORS (IMMUNOSUPPRESSANTS AND IMMUNOSTIMULATORS)

Drugs that reduce the activity of the immune system are called immunosuppressants. The need for immunosuppression occurs during tissue and organ transplantation (to prevent rejection) and in the development of autoimmune diseases (when the patient's immune system recognizes its own tissues as foreign). Today, we have a large number of immunosuppressants at our disposal, but their side effects are very serious.

Corticosteroids. Glucocorticoids reduce the number of lymphocytes in circulation (mostly T-lymphocytes) and the production of antibodies against a specific antigen. The synthesis of interleukins, especially interleukin 2, is reduced. When it comes to transplantation, glucocorticoids have the greatest effect if they are administered from the beginning, before an immune response to foreign tissue is even established. If an immune response has already been established, their effect is significantly weaker, but still exists. Side effects of corticosteroids are numerous (see the chapter on hormones) after long-term use. **Prednisolone**, orally, is usually used for immunosuppression. Corticosteroids are rarely used as monotherapy (only in hemolytic anemia, polymyalgia rheumatica, and idiopathic thrombocytopenia); they are usually combined with other immunosuppressants, because then the final effect is much better.

Cytostatics. Since during the immune response there is an explosive division of lymphocytes, cytostatics as drugs that interfere with the synthesis of nucleic acids can suppress the immune response. In contrast to their use in the treatment of malignant

tumors, where they are given in high doses intermittently, with breaks, as immunosuppressants they are administered in low doses, continuously. The most commonly used are **cyclophosphamide** (an alkylating agent), **azathioprine** (a prodrug that is metabolized in the body to the active drug, the antimetabolite mercaptopurine), and **methotrexate** (an antimetabolite, an analogue of folic acid).

Cyclophosphamide binds its active group (chloroethylamine) to nucleic bases in DNA and causes errors during replication. Adverse effects are a consequence of its basic pharmacological action: neutropenia, thrombocytopenia, alopecia, hemorrhagic cystitis. **Azathioprine**, as a precursor of mercaptopurine, also interferes with normal DNA synthesis. Mercaptopurine, as a false nucleotide, is incorporated into the DNA of rapidly dividing cells, so that errors occur during re-replication and cell death. Mercaptopurine also damages blood lineages, leading to anemia, leukopenia, and thrombocytopenia, and can also damage the liver. Azathioprine is also converted in the body to thioinosinic acid, which inhibits the synthesis of inosinic acid, a precursor of adenylic and guanylic acids. Azathioprine is well absorbed after oral administration; it is metabolized in the liver, and the metabolites are excreted in the urine. The half-life is about 5 hours. Azathioprine is used together with corticosteroids to prevent rejection of liver and kidney transplants, as well as to treat rheumatoid arthritis and Wegener's granulomatosis. The main side effects are bone marrow suppression, gastrointestinal complaints, increased susceptibility to infections, and carcinogenicity. **Methotrexate** is a folic acid analog that blocks dihydrofolate reductase, reduces the synthesis of tetrahydrofolic acid, and interferes with the functioning of enzymes whose cofactor is methyltetrahydrofolic acid. The most important enzyme in this group is thymidylate synthetase, the blockade of which prevents the formation of thymidylate, one of the 4 nucleotides necessary for DNA synthesis. Methotrexate also causes anemia, leukopenia, and thrombocytopenia.

Mycophenolate mofetil is a newer cytotoxic immunosuppressant that inhibits guanosine synthesis. It is used to prevent rejection of kidney and heart transplants in the first 6 months after surgery, often in combination with cyclosporine and corticosteroids, and to prevent and treat graft-versus-host disease after hematopoietic stem cell transplantation. It is currently more effective than all other immunosuppressants for this indication. Recently, mycophenolate mofetil has also been used to treat rheumatoid arthritis, lupus nephritis, and inflammatory bowel disease. It causes bone marrow damage and increases the incidence of skin and lymphatic tissue cancers. It is well absorbed after oral administration; it is metabolized in the liver to the active form – mycophenolic acid.

As can be seen, when cytostatics are used as immunosuppressants, a weekly control of the patient's blood count is necessary. If there is a sudden drop in the number of leukocytes or platelets, discontinuation of therapy is indicated.

Antibiotics (calcineurin inhibitors). Not so long ago, it was shown that the products of some microorganisms can have an immunosuppressive effect. **Cyclosporine**, a peptide antibiotic (a cyclic peptide with 11 amino acids) soluble in fat, blocks the differentiation of T-lymphocytes in the early stages of the establishment of the immune response. It binds to the cytoplasmic protein, cyclophilin; this complex inhibits the enzyme calcineurin phosphatase, which leads to a decrease in the synthesis and release of many cytokines, such as interleukins 2, 3 and 4, interferon alpha and tumor necrosis factor. Today it is considered the drug of choice in preventing transplant rejection (usually together with corticosteroids), but is also used to treat rheumatoid arthritis, systemic lupus erythematosus, psoriasis and uveitis. It is administered intravenously or orally, and about 50% of the administered drug is absorbed; It is metabolized in the liver and eliminated via the bile (dose is 15 mg/kg). However, it has a pronounced nephrotoxic effect, so urine and serum creatinine levels must be monitored during therapy. In addition, it causes hyperglycemia, hyperlipidemia, hirsutism and mild hepatitis. In the same group of antibiotics, there is a newer drug, **tacrolimus**. Its mechanism of action and side effects are similar to those of cyclosporine. It is used to prevent transplant rejection when other drugs fail, but also in other indications for which cyclosporine is used. It is administered intravenously or orally.

Mammalian target of rapamycin (mTOR) inhibitors. The mammalian target of rapamycin is a key element of a complex signaling system that regulates cell growth, metabolism and proliferation. When this site is blocked, the stimulatory effect of cytokines on lymphocytes will be blocked, which disrupts the immune system. Drugs that block the rapamycin binding site are **sirolimus, temsirolimus, and everolimus**. Sirolimus is used alone or in combination with other immunosuppressants to prevent acute transplant rejection and to prevent and treat graft-versus-host disease after hematopoietic stem cell transplantation. Some types of coronary stents are also impregnated with sirolimus, which are implanted in severe forms of coronary atherosclerosis; due to its antiproliferative effect, sirolimus prevents stent clogging. Everolimus is as effective as sirolimus, but it has better bioavailability. Temsirolimus is not used as an immunosuppressant. All inhibitors of the rapamycin binding site lead to severe myelosuppression, hepatotoxicity, and hypertriglyceridemia**.**

Thalidomide inhibits angiogenesis, blocks the action of tumor necrosis factor alpha, stimulates T-lymphocytes, increases the production of interleukin alpha, and inhibits phagocytosis. It has been shown to be very effective in the treatment of multiple myeloma. It is also effective in the treatment of skin changes in lupus, as well as in the suppression of erythema nodosum in patients with leprosy. Thalidomide is also very toxic: in addition to its teratogenic effect, it increases the tendency to develop venous thrombosis, causes peripheral neuropathy, and hypothyroidism. **Lenalidomide** is a derivative of thalidomide that has the

same effects but less toxicity (it causes thrombosis less often, is less teratogenic). It is used to treat multiple myeloma and myelodysplastic syndrome**.**

Leflunomide is a prodrug whose metabolite inhibits pyrimidine synthesis. It is used to treat rheumatoid arthritis. It has nephro- and hepatotoxic effects. The antimalarial **hydroxychloroquine** is also useful in the treatment of rheumatoid arthritis, as it increases the pH of intracellular organelles and thus interferes with antigen processing. Hydroxychloroquine is also used to treat lupus erythematosus**.**

Antilymphocyte and antithymocyte globulins. These are preparations that contain antibodies of animal origin against lymphocytes from the blood or against lymphocytes from the thymus. They are used to prevent transplant rejection, especially if corticosteroids have proven unsuccessful. Since the blood is predominantly composed of T-lymphocytes, antilymphocyte globulin primarily suppresses cellular immunity. Side effects of these preparations include anaphylactic reaction, serum sickness, and the development of histiocytic lymphoma at the site of multiple globulin initiation.

Muromonab-(CD3) is a monoclonal antibody derived from mouse blood that binds to the CD3 antigen on T lymphocytes. The binding of muromonab to the CD3 antigen results in inhibition of T lymphocyte activation, causing them to lose their function. The drug is used to prevent rejection of kidney, liver, or heart transplants, as well as to reduce the number of T lymphocytes in the donor's bone marrow (before transplantation). Side effects include pulmonary edema, fever, vomiting, and anaphylactic reaction.

Anti-Rh factor globulin. If the mother is Rh-negative and the child is Rh-positive, mixing of the fetal and maternal blood may occur during childbirth, sensitizing the mother to the Rh factor, i.e., producing antibodies against the Rh factor. If the child is Rh-positive again in the next pregnancy, the fetus may be damaged by the mother's antibodies and develop erythroblastosis fetalis. To prevent sensitization of the mother, she should receive anti-Rh globulin (of human origin) i.m. within 72 hours of delivery. Antibodies against the Rh factor from this globulin coat the fetal erythrocytes that enter the mother's bloodstream, thus preventing sensitization**.**

Immunostimulants are drugs that enhance the immune response. They are used to stimulate the immune response in patients with malignant tumors and in patients with congenital deficiencies of certain components of the immune system**.**

Thymosin. Thymosin is a mixture of peptides obtained by extraction from the thymus. It is used with good results in Di George syndrome (thymic aplasia and lack of cellular immunity), where it leads to the maturation of T-lymphocyte precursors).

Interferons. There are three types of interferons: alpha, beta and gamma. Within the immune response, they perform many functions that are still not fully understood. Interferon alpha is used to treat hairy cell leukemia, Kaposi's sarcoma and chronic hepatitis B and C. Side effects of interferon alpha are: flu-like syndrome, depression (with suicidal tendencies), granulocytopenia, cardiovascular disorders (hypotension, hypertension, arrhythmias), nephrotoxicity and hepatotoxicity. Interferon beta-1b is used to treat relapsing multiple sclerosis (only if the patient has had at least 2 neurological exacerbations in the last 2 years) and interferon gamma is used to treat chronic granulomatous diseases. Side effects of interferon beta are: flu-like syndrome, irritation at the injection site, depression (with suicidal tendencies), convulsions, myelosuppression and menstrual disorders. Allergic reactions can occur to all types of interferon**.**

Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte-colony-stimulating factor (G-CSF). These are cytokines that stimulate the proliferation of granulocytes and macrophages in the bone marrow. They are used to restore the bone marrow after intensive cytostatic therapy.

Interleukin 2 is a cytokine that promotes the proliferation, differentiation and clustering of T and B lymphocytes, and natural killer cells. It is administered intravenously to patients with AIDS, kidney cancer or melanoma, with the simultaneous administration of lymphocytes and killer cells from the patient, which have been previously maintained in vitro and exposed to interleukin 2. The effect of this therapy is still modest. Side effects of interleukin 2 are fever, vomiting, fatigue, flushing, diarrhea, swelling and hypotension.

Levamisole. Levamisole is a synthetic drug that activates macrophages, lymphocytes and granulocytes. It is clinically used together with fluorouracil in the treatment of colorectal cancer in Dukes C stage (Dukes C; the tumor has penetrated the colon wall all the way to the serosa) because it potentiates the effect of fluorouracil. The main side effect is the occurrence of agranulocytosis**.**

The BCG vaccine is made from live, attenuated Mycobacterium bovis bacilli. Their product is muramyl dipeptide, which activates T-lymphocytes and natural killer cells. The BCG vaccine is only useful if administered intravesically for the treatment of papillary carcinoma of the bladder. After instillation through a urinary catheter, it is left in place for two hours before urination. Severe hypersensitivity reactions may occur when this drug is administered**.**

Immunoglobulins can also be used as immunostimulants. If they are isolated from the plasma of ordinary blood donors, we obtain a preparation that contains antibodies to the most common causes of human infections, and which is usually called gamma globulin. If immunoglobulins are isolated from the plasma of donors who have previously had an infectious disease or

have been vaccinated against it, then we obtain a preparation with a high titer of antibodies against that infectious disease (so-called hyperimmune globulin). Gamma globulin is given to patients with congenital humoral immunity deficiency, and to patients with idiopathic thrombocytopenic purpura or autoimmune hemolytic anemia. It has also proven useful in the treatment of autoimmune diseases such as Kawasaki disease or Guillain-Barré syndrome. Hyperimmune globulin is given to patients suffering from a severe form of the corresponding infectious disease or to bind toxins produced by microorganisms (e.g. tetanus toxin). The main side effects of immunoglobulin administration are anaphylactic reaction and hypotension.

MONOCLONAL ANTIBODIES

Monoclonal antibodies are produced from a group of B lymphocytes (clone) that originate from the same cell, so that all antibodies are identical to each other and bind to the same antigen. Monoclonal antibodies are classically produced by the so-called "**hybridoma technology**", in which B lymphocytes that produce an antibody against a specific antigen (obtained from a mouse that has been immunized with the antigen) are fused with plasmacytoma cells that are "immortal". The hybrid cells are then grown in cultures where they produce monoclonal antibodies. A more modern way of producing monoclonal antibodies is through genetic engineering, where a bacteriophage carrying the gene for the monoclonal antibody is first selected, and then it infects cultures of Escherichia coli, which then produce the desired monoclonal antibody. By manipulating genes, a monoclonal antibody can be made that is "**chimeric**", i.e., contains an antigen-specific part that is of mouse origin and an antigen-nonspecific part (Fc fragment) that is of human origin. If an even larger part of the antibody of mouse origin is replaced by fragments of human origin (in comparison to a "chimeric" antibody), such a monoclonal antibody is called "**humanized**". Both chimeric and humanized antibodies are less immunogenic when introduced into the human body, and therefore cause fewer allergic reactions. The following are the most important monoclonal antibodies that have so far entered widespread use for the treatment of various diseases.

• **alemtuzumab** (humanized antibody), binds to CD52 on B-lymphocyte leukemia cells, for the treatment of which it is used;

• **cetuximab** (chimeric antibody) binds to the epidermal growth factor receptor, and is used to treat head and neck cancer and colon cancer;

• **bevacizumab**, a humanized antibody that binds to vascular endothelial growth factor – thereby preventing angiogenesis and is used to treat metastatic colon cancer;

• **ofatumumab** is a human monoclonal antibody that binds to the CD20 molecule on B lymphocytes, and is used to treat chronic lymphocytic leukemia;

• **rituximab** is a chimeric monoclonal antibody that binds to the CD20 molecule on B lymphocytes (but to a different site than ofatumumab) – is used to treat non-Hodgkin lymphoma, chronic lymphocytic leukemia, and rheumatoid arthritis;

• **trastuzumab** is a humanized antibody that binds to the human epidermal growth factor receptor; is used to treat breast cancer;

• **adalimumab** is a human antibody that binds to tumor necrosis factor alpha, and is useful in the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, and psoriatic arthritis;

• **certolizumab** is a humanized Fab fragment that binds to tumor necrosis factor alpha, and is used in the treatment of rheumatoid arthritis and Crohn's disease;

• **etanercept** is a complex protein consisting of the Fc fragment of a human antibody and the tumor necrosis factor alpha receptor; it is used in the treatment of rheumatoid and other arthritis;

• **infliximab** is a chimeric antibody against tumor necrosis factor alpha, and is used in the treatment of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, and psoriatic arthritis;

• **basiliximab** is a chimeric antibody that binds to CD25, i.e. to the receptor for interleukin 2; it is used for the prophylaxis of acute rejection of kidney transplants;

• **daclizumab** is a humanized antibody that binds to CD25, i.e. to the receptor for interleukin 2; it is used for the prophylaxis of acute rejection of kidney transplants;

• **natalizumab** is a humanized antibody against integrins, so it interferes with the adhesion of leukocytes and their egress into the tissue; it is used for the treatment of multiple sclerosis and Crohn's disease;

• **omalizumab** is a humanized antibody against IgE antibodies, and is used for the treatment of allergic asthma;

• **tocilizumab** is a humanized antibody that binds to the receptor for interleukin 6; it is used for the treatment of rheumatoid arthritis.

CHEMOTHERAPY

Chemotherapy of malignant diseases has advanced significantly in recent decades, so that today it is possible to cure as many as 20% of all patients with malignant diseases only by using **cytostatics**, drugs that stop the growth and reproduction of malignant cells. In order to understand the mechanism of action of cytostatics, it is necessary to know the characteristics of the life cycle of a normal and malignant cell.

The life cycle of a normal and malignant cell takes place in 4 phases. In the first phase, which is designated as **G1**, the cell prepares for the replication of its DNA by synthesizing all the enzymes necessary for this process. In the next, **S** phase, DNA replication takes place, and then the **G2** phase occurs, in which all the necessary enzymes and other molecules for mitosis are synthesized, i.e. the definitive division into two cells. In mitosis, chromosomes condense, separate, and the definitive division of the mother cell into two daughter cells occurs.

Some cells continuously re-enter this division cycle, while others enter a resting phase, which is designated **G0**. Only some cells can subsequently "wake up" from the resting phase and begin dividing again. Such cells are called stem cells. All three types of cells are present in tumors: definitively differentiated cells, cells that continuously divide, and stem cells.

Cytostatics can be divided into two groups, according to whether their action is related only to a certain phase of the cell cycle or not. Those that act in all phases of the cell cycle are called **cycle-non-specific cytostatics** (e.g. alkylating agents); cytostatics that act only in one phase of the cell cycle (e.g. vincristine and vinblastine, which act only in mitosis) are called **cycle- or phase-specific drugs**. In the case of cycle-nonspecific drugs, the dose-response function is linear, i.e., with increasing dose, the number of killed malignant cells also increases. In the case of cycle-, i.e. phase-specific drugs, this function has a plateau, i.e., a constant increase in dose after a certain time will not be accompanied by an increase in the number of killed cells.

Kinetics of malignant tumor growth

The rate at which a malignant tumor grows depends on several factors, the most important of which are: (1) the length of the cell cycle, (2) the rate at which cells die, and (3) the percentage of cells that are in the phase of active division. Usually, the rate of tumor growth can be represented by the so-called Gompertz curve, which has a plateau. Namely, tumors grow faster when they are smaller, and later growth slows down, because due to the compromise of tumor vascularization, its cells die more and more. Since the body is not able to fight malignant cells on its own as it can with microorganisms, the use of cytostatics must achieve complete destruction of all malignant cells. Therefore, cytostatics are usually used in combinations, and in a pulsed manner, i.e., they are given at short intervals in high doses, and then a break of about 3-4 weeks is allowed, so that the patient can recover from side effects. This achieves the maximum effect on the tumor, while preventing the emergence of resistance of malignant cells to cytostatics.

When combinations of cytostatics are used, cytostatics with different mechanisms of action and with different types of side effects are always used, in order to achieve the greatest possible effect with the least toxic effect on the patient's body.

It is extremely important to use appropriate doses of cytostatics: using lower doses than recommended significantly reduces the effect of the drug on the tumor, while using higher doses leads to unacceptable toxic effects on the patient's body.

Resistance of malignant cells to cytostatics

There are several mechanisms for the development of resistance of malignant cells to cytostatics. The basic form of resistance is a direct consequence of the phase in which the cell is. For example, cells that are in the resting phase are completely resistant to antimetabolites, because their effect is most pronounced in the S phase of the cell cycle. Another possibility for the development of resistance is the localization of cells in areas that drugs cannot reach (e.g. in the subarachnoid cerebrospinal space). Then the cells simply do not respond to cytostatics, because they do not come into contact with them.

However, the so-called acquired resistance is of greater importance, i.e. resistance as a result of exposure of the tumor to cytostatics. It is usually characterized by cross-resistance, i.e. after exposure to one drug, tumor cells become resistant to the entire group of cytostatics that includes the applied drug. The most common mechanism of this form of resistance is the **overexpression** of the gene encoding the transmembrane glycoprotein P. Glycoprotein P is a transmembrane pump that normally effluxes exogenous or endogenous toxins from the cell. This pump is normally found in renal tubule cells, the epithelium of the jejunum and colon, the epithelium of the biliary tract, and the capillaries of the brain and testes. In tumors exposed to cytostatics, the expression of this pump is induced, as a result of which the tumor cells very quickly and easily efflux cytostatics before they have an effect on functional molecules.

This type of resistance, where there is an overexpression of glycoprotein P, is particularly common with the use of the following cytostatics: anthracycline antibiotics, vincristine and vinblastine, paclitaxel, etoposide, mitomycin, and plicamycin. It should be noted that if resistance to one of these cytostatics occurs, resistance to all of them practically occurs.

According to the site of action and chemical structure, cytostatics can be classified into several groups:

Alkylating agents
Antimetabolites
Antibiotics
Plant alkaloids
Enzymes
Hormones
Others.

Alkylating agents

These substances have alkyl radicals in their molecules, which easily bind to nitrogen atoms in purine and pyrimidine bases of nucleic acids. They most often bind to nitrogen at position 7 in the purine nucleus (guanine). The consequence of alkylation of guanine can be cross-linking of 2 DNA strands, or incorrect base pairing (guanine pairs with thymidine instead of cytosine). It can also lead to DNA strand breakage and cell death.

Alkylating agents act on cells **in all phases of their life cycle**. Therefore, in addition to the treatment of leukemia and lymphoma, they are used for the treatment of solid tumors in which a large part of the cells are in the resting phase (G0). The most important groups of alkylating agents are: nitrogenous bases, nitrosoureas, alkyl sulfonates, ethyleneimines and triazenes.

Nitrogen chelators. The most important representatives of this subgroup are **mechlorethamine, cyclophosphamide, ifosfamide, chlorambucil and melphalan**. **Mechlorethamine** was the first cytostatic to enter general use. It was obtained as a derivative of the sulfur chelator poison in 1940. It contains a reactive cyclic ethyleneammonium ion. It is very short-lived in the body (half-life is about 10 minutes), is metabolized in the liver, and the metabolites are excreted in the urine. It is used for the treatment of Hodgkin's disease, within the MOPP protocol.

Cyclophosphamide has the broadest spectrum of action of all alkylating agents. After oral or parenteral administration, cyclophosphamide is converted by the cytochrome P450 system into the active metabolites **phosphoramide and acrolein**. While cyclophosphamide is 15% bound to plasma proteins, its metabolites are as much as 50% bound to the same proteins. Both cyclophosphamide and its metabolites are excreted in the urine, where they irritate the bladder mucosa, causing hemorrhagic cystitis. Large doses of cyclophosphamide can lead to decreased renal water excretion, and thus hyponatremia.

Ifosfamide behaves similarly to cyclophosphamide in the body; it is also converted to the active metabolite. It is more effective than cyclophosphamide in germ cell carcinomas and sarcomas. Like cyclophosphamide, ifosfamide causes hemorrhagic cystitis; To prevent this side effect, ifosfamide is administered with **mesna**, a substance with thiol (SH) groups, which binds to the cytostatic and its metabolites in the urine, preventing binding to transitional epithelium cells.

Chlorambucil is a substance with a benzene ring, which is used as a palliative therapy for chronic hematological malignancies (e.g. chronic lymphocytic leukemia). **Melphalan is an amino acid derivative of mechlorethamine**. It is used in the palliative therapy of ovarian, breast, or multiple myeloma carcinoma.

Nitrosoureas. These drugs are most often liposoluble (**lomustine** – CCNU, **carmustine** – BCNU, **semustine** – methyl-CCNU), which allows them to easily penetrate the central nervous system and achieve high concentrations there. On the other hand, they are very chemically unstable, and are easily degraded to chloroethyl diazohydroxide and isocyanate (T1/2 = 10 minutes), active metabolites that perform both alkylation and carbamoylation of DNA of tumor cells. Due to their rapid degradation, these drugs cannot be administered orally. They are used for the treatment of primary brain tumors (astrocytomas, oligodendrogliomas). Their characteristic side effect is pulmonary fibrosis.

The nitrosoureas also include **streptozocin**, a water-soluble substance. It selectively causes a deficiency of nicotinamide adenine dinucleotide (NAD) in pancreatic islet cells. Therefore, it is used for the treatment of pancreatic beta-cell tumors (nonidioblastomas). It is administered only intravenously, and is rapidly degraded (T1/2 = 10 minutes). It can damage the renal tubules.

Temozolomide is another alkylating agent that penetrates the central nervous system well. It is used to treat primary brain tumors, and its efficacy is being tested in the treatment of brain metastases and metastatic melanoma. It is much better tolerated than lomustine, carmustine, and semustine.

Alkyl sulfonates. The only representative of this group used in practice is **busulfan**. It is administered orally; it is well absorbed, but is rapidly degraded (T1/2 = 5 minutes), so that the metabolites are excreted in the urine. It is used for the palliative treatment of chronic myeloid leukemia.

Ethyleneimines. The representative of this group used clinically is **thiotepa**. This drug is directly administered into the bladder through a urethral catheter for the treatment of multifocal bladder carcinoma.

Triazenes. **Dacarbazine** is the only representative with clinical significance. It methylates DNA and RNA of tumor cells. After oral administration, the drug is first distributed (T1/2 = 19 minutes), and then metabolized and eliminated (T1/2 = 5 hours) by tubular secretion. It is the best drug for the fight against metastatic melanoma (it causes remission in 20% of patients), and is also used for sarcomas and Hodgkin's disease.

Antimetabolites

Antimetabolites are structural analogues of natural molecules that participate in the synthesis of DNA and RNA. They act by competing with natural molecules for active sites on enzymes, or simply completely replacing natural molecules in the synthesis process. Therefore, they are most active in the **S** phase, and practically do not affect tumor cells that are in the resting phase. They are used to treat malignant tumors that have a large fraction of cells in the growth phase, which are actually mainly hematological malignancies. They can be classified into three subgroups: folate analogues (methotrexate), purine analogues (mercaptopurine, thioguanine, fludarabine, cladribine, pentostatin) and pyrimidine analogues (5-fluorouracil, capecitabine – which is metabolized to 5-fluorouracil, cytarabine, gemcitabine).

Methotrexate. Methotrexate competitively inhibits the binding of folic acid to the enzyme dihydrofolate reductase. This **prevents the formation of tetrahydrofolic acid**, and from it also N5, N10 – methylenetetrahydrofolic acid (**leucovorin, folinic acid**), a necessary cofactor for the synthesis of thymidylate, purine, methionine and glycine. Methotrexate is well absorbed after oral administration, and is 50% bound to plasma proteins. Elimination occurs in 3 phases: the first distribution, initial and late elimination phases. The drug is excreted by the kidneys, by glomerular filtration and tubular secretion.

Interestingly, methotrexate accumulates in tumor cells in the form of polyglutamate conjugates, which ensures a prolonged effect of the drug.

Methotrexate is used to treat acute lymphoblastic leukemia, Burkitt's lymphoma, and choriocarcinoma. It can also be administered intrathecally (into the subarachnoid space) to prevent meningeal metastases in acute lymphoblastic leukemia.

A specific acute side effect of methotrexate is damage to the renal tubules; long-term use leads to cirrhosis of the liver. If methotrexate is overdosed, the patient can be saved from side effects by administering folinic acid.

Probenecid, salicylates, and sulfonamides inhibit the tubular secretion of methotrexate in the kidney.

Pemetrexed and pralatrexate also inhibit dihydrofolate reductase, with pemetrexed also blocking thymidylate synthetase. Pemetrexed is used to treat non-small cell lung cancer, and pralatrexate is used for refractory T-cell lymphoma. Pemetrexed and pralatrexate are administered together with folic acid and vitamin B12 to prevent bone marrow toxicity.

Thioguanine. Thioguanine is a prodrug that is converted to thioguanosine monophosphate by hypoxanthine guanine phosphoribosyltransferase (HGPRTase). This substance is further converted to thioguanosine triphosphate, the active form of the drug that is incorporated into DNA or RNA, leading to incorrect protein coding. Thioguanine is slowly absorbed; it is metabolized in the liver, and the metabolites are excreted in the urine (about 40% of the administered drug is excreted in 24 hours). It is most effective in acute myeloid leukemia.

Mercaptopurine. The mechanism of action of mercaptopurine is very similar to that of thioguanine; it must also be activated by hypoxanthine guanine phosphoribosyltransferase. The drug is administered orally. About 20% of the drug in plasma is bound to proteins, and the drug does not penetrate the central nervous system. It is metabolized by the enzyme xanthine oxidase. The half-life is only about 20 minutes. Mercaptopurine is used to treat acute leukemia, primarily lymphoblastic leukemia.

Fludarabine is related to the antiviral drug vidarabine. In cells, it is converted to the active metabolite 2-fluoro-ara-adenosine triphosphate, which inhibits DNA polymerase, a key enzyme in DNA synthesis. It is used to treat chronic lymphocytic leukemia.

Pentostatin inhibits the enzyme adenosine deaminase, which is involved in the breakdown of adenosine. Due to the blockade of this enzyme, adenosine and deoxyadenosine triphosphate accumulate, which have a toxic effect on lymphocytes. Pentostatin is very effective in the treatment of hairy cell leukemia (remission in 90% of patients). **Cladribine** is also used for the same purpose.

Gemcitabine is converted in cells to the active metabolite difluoro-deoxycytidine triphosphate, which interferes with DNA synthesis. It is used in intravenous infusion for the treatment of metastatic pancreatic cancer, as well as for small cell lung cancer.

Cytarabine, after conversion to the triphosphate form, inhibits DNA polymerase of tumor cells. It is active against acute myeloid leukemia. It is administered intravenously, and is rapidly metabolized (T1/2 = 10 minutes) to uracil arabinoside, which is excreted in the urine.

Fluorouracil (5-fluorouracil) is converted in tumor cells to the active metabolite 5-fluoro-2`deoxyuridine-S`-phosphate, which then inhibits thymidylate synthetase, an enzyme that synthesizes thymidylate (dTMP), which is necessary for the formation of DNA. In this reaction, the cofactor is folinic acid, which also enhances the action of fluorouracil. Fluorouracil is administered intravenously and is rapidly metabolized in the liver (T1/2 = 10 minutes); only 20% of the drug is excreted in the urine.

Fluorouracil is used primarily for the treatment of breast and gastrointestinal cancers. In the form of a cream, it is used locally for the treatment of premalignant keratoses and skin.

Capecitabine is an oral prodrug that is converted to 5-fluorouracil in cells. It is used, like fluorouracil, to treat breast cancer and metastatic colon cancer, but only when patients have not responded to conventional therapy. A number of patients who receive this drug develop a painful, red rash on the palms and soles of the feet.

Azacitidine is a nucleoside analogue of cytidine. It is used to treat acute myeloid leukemia and myelodysplastic syndromes. After phosphorylation, it is incorporated into RNA and interferes with its function.

Antitumor antibiotics

These drugs are called antibiotics because they were discovered in nature as products of microorganisms, which they use to defend themselves against other organisms. Antibiotics **intercalate** between two adjacent DNA bases (especially between guanine and cytosine, and guanine and thymine), which prevents the normal functioning of DNA. In addition, they inhibit DNA **topoisomerases I and II** (see box on topoisomerases). The most widely used antitumor antibiotics are doxorubicin, daunorubicin, idarubicin, bleomycin, mitomycin, dactinomycin and plicamycin.

Doxorubicin and daunorubicin are products of the bacterium Streptomyces peucetius. While daunorubicin has a beneficial effect only on acute leukemias, doxorubicin has a very broad spectrum of action on various malignant tumors. Doxorubicin is therefore used in practice by far more. Because it has the property of generating free radicals, doxorubicin exhibits specific **cardiotoxicity** (arrhythmias, negative inotropic effect), and can re-induce an inflammatory reaction in areas previously exposed to ionizing radiation (radiation recall reaction). Due to its distinctly red color, the urine of patients receiving it will be reddish, and hyperpigmentation of the nail bed and skin folds may occur.

Doxorubicin is administered intravenously. It is metabolized in the liver to conjugated metabolites, which are excreted in the bile.

Idarubicin differs from daunorubicin and doxorubicin only in the lack of one methoxy group. It is similar to doxorubicin in all respects, except that it is more lipophilic and somewhat more potent.

Bleomycin is a glycopeptide antibiotic that is effective against advanced testicular cancer. It is administered parenterally. Bleomycin is inactivated by the enzyme bleomycin hydrolase, which is found in almost all tissues except the lungs and skin. Therefore, bleomycin has serious side effects in these tissues (pulmonary fibrosis, skin thickening, hyperpigmentation). Many patients react to bleomycin administration with an elevated body temperature.

Mitomycin, after penetrating the tumor cell, is activated by a reduction process. It is administered intravenously and does not penetrate the central nervous system. It is used in the palliative treatment of gastric, pancreatic, and colon cancer.

Dactinomycin is an antibiotic active against tumors in children: Wilms' tumor, Ewing's sarcoma, and rhabdomyosarcoma.

Plicamycin (mithramycin) is not generally used to suppress malignant tumors, but rather to treat severe hypercalcemia. It has the unique property of inhibiting bone resorption, thereby lowering serum calcium levels..

Cytostatics of plant origin

There are several types of cytostatics of plant origin, and all of them are characterized by significant toxicity.

Alkaloids from the plant Vinca rosea (**vincristine, vinblastine and vinorelbine**) act by binding to tubulin, a protein that builds microtubules, and preventing its incorporation into the mitotic spindle. In this way, they prevent mitosis of malignant cells,

and thus tumor growth. These drugs are metabolized in the liver, and excreted in the bile. Vincristine is used to treat acute lymphoblastic leukemia, Hodgkin and non-Hodgkin lymphomas, and solid tumors in children. Vinblastine successfully acts on testicular cancer, and vinorelbine on advanced non-small cell lung cancer. Vincristine specifically causes **neuropathy** (because microtubules are also required for axonal transport).

Etoposide and teniposide are toxins from the plant Podophyllum peltatum that inhibit the enzyme topoisomerase II, which prevents DNA synthesis and thus malignant cell division. Etoposide is effective against germ cell tumors of the testis and ovary, lymphomas, small cell lung carcinoma, and acute leukemia. Teniposide is most useful in the treatment of acute lymphoblastic leukemia. **Paclitaxel and docetaxel** are semisynthetic derivatives of natural substances from the plant Taxus baccata, which also interfere with the functioning of the mitotic spindle, but by a slightly different mechanism than the alkaloids from the plant Vinca rosea. In addition, they induce apoptosis of malignant cells. Paclitaxel is primarily metabolized in the liver; very small amounts of the drug are excreted in the urine. Both drugs are active against breast, lung, ovarian, and head and neck cancers. Specific toxicity is reflected in the development of peripheral neuropathy.

The alkaloid **camptothecin** has been isolated from the plant Camptotheca acuminata, whose semisynthetic derivatives **irinotecan and topotecan** inhibit topoisomerase I, thus preventing DNA replication in malignant cells. Topotecan is used to treat advanced ovarian cancer, and irinotecan is used to treat metastatic colon cancer.

Enzymes

L-asparaginase is an enzyme of bacterial origin that breaks down L-asparagine into aspartate and ammonium. When administered intravenously to patients, it remains in the bloodstream and leads to asparagine deficiency. Since acute lymphoblastic leukemia cells cannot synthesize asparagine themselves and depend on asparagine from the blood, they are deprived of this amino acid and cannot divide.

After infusion, the drug remains in the blood for a day or two. It is gradually broken down by serum proteases and phagocytized by cells of the reticuloendothelial system. Asparaginase can cause severe allergic reactions, liver damage (severe hepatitis in about 5% of patients), drowsiness, confusion, pancreatitis (5-10% of patients), and hyperglycemia. However, asparaginase is not toxic to the bone marrow, so it can be combined with other cytostatics.

Hormones

Hormone-dependent tumors can be treated quite successfully with drugs that bind to hormone receptors (most often blocking them, and sometimes overactivating them). The most important drugs in this group are those that bind to sex hormone receptors.

Tamoxifen blocks estrogen receptors, so it can prevent the growth of breast cancer cells that have such receptors. Tamoxifen is slowly absorbed after oral administration and concentrates in tissues that have estrogen receptors (breast, ovaries, uterus). It is metabolized in the liver by hydroxylation and glucuronidation, and the resulting metabolites are excreted in the bile.

Tamoxifen induces remission of **breast cancer** with cells that have estrogen receptors in 60% of patients. The effect lasts for about a year, and in about 10% of women for several years. It is used as an additional (adjuvant) therapy in menopausal patients who have had their tumor surgically removed. The drug is well tolerated; it causes hot flashes (a feeling of warmth in the face and neck accompanied by redness of the skin) in 15% of patients, and sometimes vaginal dryness. Bone pain accompanied by hypercalcemia is rare. Aromatase is an enzyme that converts androgens originating from the adrenal gland into estrogens in adipose tissue. Thanks to this enzyme, menopausal women have sufficient amounts of estrogen, even though their ovaries have stopped functioning. **Aromatase inhibitors (anastrozole, letrozole, exemestane)** can prevent or slow the growth of breast cancer in menopausal women if the cancer cells have estrogen receptors. Until now, they have been used in patients who no longer respond to tamoxifen, but the latest clinical studies have shown that these drugs can be used instead of tamoxifen, and that the results with them are better: fewer tumor recurrences and fewer new tumors. Their side effects are moderate: accelerated osteoporosis, increased plasma lipids, pain and stiffness of the joints. Both tamoxifen and aromatase inhibitors may cause **thrombosis** as side effect.

The newest antiestrogen used in oncology is **fulvestrant,** which can cause downregulation of estrogen receptors, i.e. reduce their number. It is administered as a depot intramuscular injection, once a month, in metastatic breast cancer whose cells have estrogen receptors.

Flutamide blocks androgen hormone receptors. It is administered orally, and is used to treat prostate cancer. It is especially useful in combination with the gonadotropin-releasing hormone agonist, **leuprolide**. Leuprolide temporarily increases testosterone

secretion at the beginning of therapy, so flutamide successfully eliminates this undesirable phenomenon. Flutamide causes hot flashes and impotence.

Estramustine is a hybrid molecule, composed of estradiol and nitrogen-containing compounds. It is used to treat prostate cancer that no longer responds to estrogen-only therapy. It has the same side effects as estrogen hormones: breast tenderness, gynecomastia, hypertension, thrombophlebitis.

Leuprolide and buserelin are peptide analogues of gonadotropin-releasing hormone from the hypothalamus. When administered continuously, they prevent the release of gonadotropins from the pituitary gland, effectively leading to chemical castration. They are used for the palliative treatment of prostate cancer. They are well tolerated, causing only hot flashes.

The somatostatin analogue **octreotide** is a peptide that can inhibit the secretion of insulin, glucagon and hormones from carcinoid cells. Therefore, it is used for the treatment of metastatic carcinoid tumors and pancreatic islet carcinomas. It is administered parenterally, and has a relatively short half-life (but significantly longer than somatostatin; T1/2 = 1.5 hours). It is excreted in the urine. As a side effect, it can cause hypoglycemia or hyperglycemia.

Other cytostatics

Hydroxyurea inhibits the conversion of ribonucleotides to deoxyribonucleotides, thereby preventing DNA synthesis. It is administered orally, rapidly absorbed, and eliminated largely unchanged via the kidneys (T1/2 = 2-3 hours). Hydroxyurea is used for the treatment of chronic myeloid leukemia, both in induction and in the maintenance of remission. After prolonged administration, it causes hyperpigmentation and hyperkeratosis**.**

Procarbazine is spontaneously oxidized, generating free radicals that damage DNA. It also methylates guanine at the N7 position. The drug is rapidly and well absorbed after oral administration, and then metabolized in the liver. The drug metabolites are excreted in the urine (T1/2 = 10 minutes). It penetrates the blood-brain barrier well. It is used in the combination therapy of Hodgkin and non-Hodgkin lymphomas, as well as for small cell lung cancer.

Procarbazine has a high potential for interactions with other drugs. It potentiates the depressive effect of sedatives, and when used with alcohol, it can cause a reaction similar to disulfiram. If used together with foods rich in tyramine or with sympathomimetics, it can lead to a jump in blood pressure.

Mitotane is a drug that, after oral administration and incomplete absorption, shows a tendency to accumulate in fatty tissue, especially in the adrenal cortex. When it accumulates sufficiently, it causes necrosis of the adrenal cortex, which is a beneficial effect in people with adrenal cortex cancer. It is excreted very slowly, and causes lethargy and somnolence**.**

Hexamethylmelamine inhibits DNA and RNA synthesis in ovarian adenocarcinoma cells, by a mechanism that is still poorly understood. After oral administration, it is well absorbed, metabolized in the liver, and the metabolites are excreted in the urine.

Cisplatin is an inorganic platinum complex that binds to the N7 position of guanine and leads to cross-linking of two nucleic bases, similar to what alkylating agents do. The end result is interference with DNA replication. Cisplatin is particularly active against testicular and ovarian carcinoma. This drug remains in the human body for several days after intravenous infusion, because elimination via the kidneys is slow. Since it is eliminated via the kidneys, it concentrates there and can damage the renal tubules. It also accumulates in the perilymph of the inner ear, leading to hearing loss at high frequencies. Peripheral neuropathy has also been reported.

Carboplatin is an analogue of cisplatin, which is eliminated from the body much more quickly. Due to its faster elimination, its toxic effects on the kidney, inner ear and peripheral nerves are much less than the toxic effects of cisplatin. It is used, like cisplatin, for the treatment of testicular and ovarian tumors**.**

Mitoxantrone is chemically related to anthracycline antitumor antibiotics, so it "intercalates" into the DNA chain, interfering with its function. It is active against leukemia, lymphoma and breast cancer.

DNA Topoisomerases I and II

DNA topoisomerases are enzymes that regulate the supercoiling of human DNA. Topoisomerase I is involved in this process by breaking one strand of DNA, causing the entire DNA to bend, and then repairing the break. Topoisomerase II breaks both strands of DNA, causing the DNA to bend, and then reconnecting the two strands.

Topoisomerases are essential for the processes of DNA replication and RNA transcription, as they actually allow DNA to unwind and access other enzymes necessary for these two processes. The counterpart of human topoisomerases in a bacterial cell is the enzyme gyrase.

Two more topoisomerases, designated topoisomerase III and IV, have recently been discovered. Topoisomerase III is thought to play a significant role in the recombination process, while topoisomerase IV enables the separation of newly synthesized chromosomes.

IMMUNOMODULATORS IN THE TREATMENT OF MALIGNANT TUMORS

In addition to cytostatics, drugs that affect the human immune system can also be useful in the treatment of tumors. One group of such drugs consists of monoclonal antibodies to specific proteins on the membrane of malignant cells. **Alemtuzumab** is used to treat beta-cell chronic lymphocytic leukemia, which carry the CD52 antigen. It is a monoclonal antibody that binds to the CD52 antigen and leads to the lysis of malignant cells. The monoclonal antibody **rituximab** is used to treat follicular non-Hodgkin lymphoma, whose cells carry the CD20 antigen. Both alemtuzumab and rituximab are used only in patients who have previously been treated with cytostatics and have not responded well to them. **Trastuzumab** is a humanized monoclonal antibody that binds to the HER-2 antigen on the surface of breast tumor cells. It has recently been shown that early administration of this antibody (already after breast removal) can significantly improve the prognosis of patients, i.e., prolong survival.

The side effects of alemtuzumab are numerous and serious: neutropenia, anemia, thrombocytopenia, lymphopenia, increased frequency of infections (which is why patients receive antibiotic prophylaxis) and a flu-like condition during drug administration.

Alemtuzumab is used as an intravenous infusion, three times a week, for a total of 12 weeks.

The side effects of rituximab are: a flu-like condition during drug administration (the so-called cytokine release syndrome), worsening of angina pectoris, arrhythmias and heart failure. Rituximab is also administered as an intravenous infusion.

Trastuzumab sensitizes the myocardium to the toxic effects of other cytostatics, especially doxorubicin. When administered as an intravenous infusion, this drug can cause hypotension, facial flushing, and bronchoconstriction.

Another monoclonal antibody that has found its place in the treatment of malignant tumors is **bevacizumab**. It is the first antiangiogenic drug, which binds to vascular endothelial growth factor, and thus prevents the growth of blood vessels in the tumor. Reduced blood flow prevents further tumor growth, so bevacizumab is approved for use in metastatic **colon cancer**, as an adjunct to cytostatic therapy. The most common side effects of this drug are hypertension and proteinuria, but due to its antiangiogenic effect, it can make wound healing difficult in some patients and lead to bleeding or intestinal perforation.

Cetuximab and panitumumab are monoclonal antibodies that bind to the epidermal growth factor receptor on malignant cells, blocking it, and thus stopping tumor growth. They are used to treat head and neck cancer, and metastatic colorectal cancer that has the KRAS form of the RAS protein, a mediator of cell proliferation and differentiation.

Pembrolizumab is a humanized monoclonal antibody that binds to PD-1, a programmed death receptor on T lymphocytes, and prevents the binding of the ligands PD-L1 and PD-L2 to this receptor. These ligands are otherwise produced by tumor cells, which in this way lead to apoptosis of T lymphocytes and a weakening of the immune response. Pembrolizumab prevents this immunosuppressive effect of the tumor, and thus prevents its spread, i.e., metastasis. Due to this mechanism of action, pembrolizumab has a very broad spectrum of action, i.e., it is used to treat several types of malignant tumors: lung, kidney, melanoma, head and neck tumors, Hodgkin lymphoma. etc. The main side effects of pembrolizumab are autoimmune inflammations of various organs – lungs, colon, liver, kidneys, skin, etc.

Levamisole is an antiparasitic drug that enhances the defense functions of T-lymphocytes. If used together with fluorouracil in patients who have just undergone surgery for colon cancer, it significantly prolongs survival. It causes loss of appetite and a flu-like syndrome.

Interferon alfa-2b has shown remarkable effect in hairy cell leukemia, where it causes remission in about 70% of patients. As a side effect, it causes elevated temperature and a flu-like syndrome.

Interleukins also have their place in the treatment of malignant tumors. **Aldesleukin** is a human recombinant interleukin 2, which enhances the cytotoxicity of T-lymphocytes, induces the activity of natural killer cells and causes the production of interferon gamma. This drug can induce remission in about 15% of patients with renal cell carcinoma. At the same time,

aldesleukin is very toxic, as it can cause capillary leak syndrome, with hypotension, pulmonary edema, and increased cardiac workload. **Thalidomide** was widely used as a sedative in the 1960s, but its use was then abruptly discontinued due to its teratogenic effect. A large percentage of children born to mothers who used thalidomide during pregnancy developed phocomelia, a congenital anomaly in which the limbs were completely stunted. It is the inhibitory effect of thalidomide on the formation of new blood vessels (angiogenesis) that led to phocomelia. In addition to inhibiting angiogenesis, thalidomide also has strong anti-inflammatory and immunomodulatory effects. Several years ago, the positive effects of thalidomide were observed in certain tumors, and it is now used to treat multiple myeloma, usually together with dexamethasone. Talidomid is very toxic; in addition to its teratogenic effect, it causes peripheral **neuropathy, hypothyroidism, and increases the risk of deep vein thrombosis**. That is why today, along with thalidomide, some oral anticoagulants are prescribed. In the search for equally effective but less toxic drugs, thalidomide derivatives that retain immunomodulatory effects have been synthesized, such as **lenalidomide**. It is successfully used in the treatment of myelodysplastic syndrome in patients with a 5q31 deletion.

NEW DRUGS AGAINST MALIGNANT DISEASES

Tyrosine kinase inhibitors

Imatinib is a blocker of an abnormal enzyme called tyrosine kinase, which is produced in cells of chronic myeloid leukemia. This type of leukemia has an abnormal chromosome 22, which is caused by a translocation of two chromosomes (called the Philadelphia chromosome), and on which there is a gene that codes for an abnormal tyrosine kinase. Imatinib is used in patients with chronic myeloid leukemia who have not responded to previous therapy with interferon alpha. It is very effective: it leads to complete remission in as many as 88% of patients, and in 30% of patients, cells with the Philadelphia chromosome are lost (cytogenetic remission).

This drug also works well on gastrointestinal stromal sarcoma, whose cells contain an abnormal tyrosine kinase. This type of tumor does not normally respond to other forms of therapy.

Imatinib is well tolerated. Adverse effects include nausea, vomiting, edema, cramps, muscle pain, fever, and fatigue. Neutropenia, thrombocytopenia, and liver damage are rare.

Imatinib is administered orally and is well absorbed. It is metabolized in the liver via the CYP3A4 cytochrome P450 isoform, and 25% of the drug is excreted unchanged in the urine. **Nilotinib and dasatinib** act by a similar mechanism to imatinib, and are used for the same indications**.**

Gefitinib and erlotinib inhibit the tyrosine kinase that is actually the intracellular part of the transmembrane receptor for epidermal growth factor (rEFR). They can lead to remission of advanced lung cancer, provided that its cells have rEFR on their membrane. Bronchoalveolar carcinoma, which exhibits particularly high rEFR, responds particularly well to these drugs. Both drugs are well tolerated; they cause only rash and diarrhea.

Sunitinib and pazopanib are inhibitors of vascular endothelial growth factor-related and platelet-derived growth factor-related tyrosine kinases, which are used to treat locally advanced or metastatic renal cell carcinoma. They cause redness and blistering of the palms and soles, as well as anemia, leukopenia, and thrombocytopenia**.**

Sorafenib inhibits serine/threonine and tyrosine kinases. It is used to treat hepatocellular carcinoma and renal cell carcinoma.

Proteasome inhibitors

Proteasomes are tubular protease complexes in the cytoplasm of cells that degrade proteins that have performed their function or are damaged. All proteins that are marked with a small peptide called ubiquitin enter these tubules, and these are the proteins that have performed their function or are damaged. After entering the tubules, the marked proteins are broken down into amino acids. With the help of proteasomes, the cell gets rid of unnecessary proteins.

Bortezomib inhibits the proteasomes of malignant cells, so that unnecessary proteins accumulate in them and normal functions are disrupted, i.e., the malignant cell dies. It is used to treat **multiple myeloma** that has not responded to at least two types of therapy. Bortezomib can cause peripheral neuropathy, bone marrow suppression, and hypersensitivity reactions.

Vitamin A derivatives

Tretinoin accelerates the differentiation and reduces the proliferation of cells in acute promyelocytic leukemia, thereby improving the general condition of patients with this disease. It is used in combination with drugs that have a cytolytic effect on these cells, such as arsenic trioxide. Arsenic trioxide induces remission in 70% of patients with acute promyelocytic leukemia who have not responded to other types of therapy.

Another vitamin A derivative, **bexarotene,** selectively activates the retinoid "X" receptor, thereby reducing the proliferation of cells in cutaneous T-cell lymphoma (e.g. mycosis fungoides)**.**

Antibodies bound to cytostatics or ionizing radiation emitters

This type of therapy is a so-called **"targeted"** pharmacological therapy, where an antibody binds to a defined site on a malignant cell, which is then attacked by a "deadly cargo" carried by the antibody (toxin, cytostatic or radio-emitter).

Ibritumomab tiuxetan is an antibody that binds to the CD20 antigen on non-Hodgkin lymphoma cells, and carries yttrium-90, a pure beta emitter with a half-life of 64 hours and a radiation range of 5 mm. This drug leads to remission in 80% of patients who have become refractory to other types of therapy. The main side effect of this drug is bone marrow suppression.

Tositumomab is another antibody that binds to the CD20 antigen, and carries radioactive iodine 131. It is also used to treat non-Hodgkin lymphoma, and has the same side effects as ibritumomab tiuxetan.

Denileukin diftitox is not an antibody, but a hybrid protein composed of part of diphtheria toxin and part of interleukin 2. It binds to cells that have the receptor for interleukin 2 (CD25), and kills them in the same way as diphtheria toxin. It is used to treat cutaneous T-cell lymphomas that are resistant to standard therapy and whose cells have the CD25 receptor. Denileukin diftitox can cause allergic reactions and delayed edema of the lungs and extremities.

Gemtuzumab ozogamicin is an antibody that binds to the CD33 antigen, and carries the antitumor antibiotic **calicheamicin**. It is used to treat patients over 60 years of age who have relapsed acute myelogenous leukemia, provided that the cells express the CD33 antigen. Gemtuzumab ozogamicin causes bone marrow suppression and causes reactions when given into a vein.

Adverse effects of cytostatics

Due to their mechanism of action, cytostatics have significant side effects on all rapidly dividing tissues in the human body. They actually act on these tissues as well as on tumors: they lead to the death of a number of cells. In addition, they have certain specific side effects, which are characteristic of each cytostatic in particular. A good knowledge of the side effects of cytostatics is a prerequisite for their proper use. It is particularly important that general practitioners know the side effects of cytostatics, in order to recognize them in time in their patients and respond adequately.

Nausea and vomiting occur very often with the use of cytostatics. They can be anticipatory in nature (occurring before taking the drug), acute in nature (when they occur within 24 hours of receiving therapy) or delayed (when they occur after 24 hours of receiving therapy). Although they can occur with the use of all cytostatics, nausea and vomiting most often occur with the use of cisplatin, dacarbazine, cyclophosphamide, methotrexate, doxorubicin and mitoxantrone.

To prevent nausea and vomiting with cytostatics with a lower emetogenic potential, **domperidone** or one of the phenothiazines is used primarily, at least one hour before the start of the cytostatic administration, and its administration is continued for up to 24 hours after the administration of chemotherapy. If the vomiting is of the anticipatory type, the administration of lorazepam is indicated, and if the vomiting is of the delayed type, it should be given with domperidone and dexamethasone.

If cytostatics with high emetogenic potential are used, the drugs of choice for preventing vomiting are serotonin 5HT3 receptor blockers: **ondansetron, granisetron, dolasetron and palonosetron**. Ondansetron is administered parenterally (32 mg before chemotherapy, then the same dose is repeated after 24 hours) or orally (8 mg every 8 hours). 5HT3 receptor blockers are more effective if they are given together with dexamethasone (6-10 mg before chemotherapy).

When using cisplatin and other most emetogenic cytostatics, the combination of 5HT3 receptor blockers and **dexamethasone is added to the neurokinin-1 receptor blocker aprepitant**, through which substance P acts in the body. The drug is administered for a total of three days, starting immediately before the start of chemotherapy.

Bone marrow suppression is a side effect of all cytostatics except vincristine and bleomycin. Anemia occurs only after several cycles of chemotherapy, due to the long life of erythrocytes in the peripheral blood (about 120 days). In contrast, leukopenia reaches a maximum 7 to 10 days after the administration of cytostatics, and it takes about 20 days for the white blood cells to recover. Some cytostatics (melphalan, carmustine and lomustine) have a **delayed leukopenic effect**, so that the lowest number of leukocytes is registered after about 11-14 days.

If the number of leukocytes falls below 1 x 109/L and the patient develops a fever, then an infection is most likely present, so the use of broad-spectrum antibiotics is advised. In milder infections, a combination of ciprofloxacin (oral) and amoxicillin with clavulanic acid (oral) is used, and in more severe infections, 3rd or 4th generation cephalosporins are administered parenterally. In more severe neutropenia, recovery can be accelerated by the use of granulocyte-macrophage colony-stimulating factor (GM-CSF, sagramostim) or granulocyte colony-stimulating factor (G-CSF, filgrastim). These factors stimulate the proliferation and differentiation of bone marrow cells into granulocytes and macrophages. Filgrastim also promotes the functioning of mature granulocytes. A side effect of these growth factors is bone pain, due to the sudden proliferation of bone marrow cells.

Alopecia regularly occurs with cytostatic therapy, but is reversible and does not require pharmacological treatment.

Inflammation of the oral mucosa with ulceration most often occurs with the use of **methotrexate, fluorouracil and anthracyclines.** It can be prevented by good oral hygiene and sucking on ice cubes during the fluorouracil infusion. When methotrexate is used, inflammation of the oral mucosa can be shortened and alleviated by the use of folinic acid. Special preparations that coat the ulcerations are also used.

Hyperuricemia occurs as a complication of the treatment of leukemia and lymphoma, due to the high production of uric acid. It can be prevented by adequate hydration of the patient and the use of allopurinol, starting one day before the use of cytostatics. Allopurinol inhibits the enzyme xanthine oxidase and thus prevents the production of uric acid. However, in more severe cases, where the burden of malignant cells is very high, it is better to use **rasburicase**. Rasburicase is a genetically engineered enzyme called urate oxidase, which oxidizes uric acid into more soluble compounds. Urate oxidase does not exist in humans, but is present in some other mammals. When administered to patients undergoing chemotherapy, rasburicase effectively reduces uric acid levels.

Rasburicase is given once daily as an intravenous infusion for 6-7 days. The half-life of rasburicase is 20 hours; it is degraded by numerous peptidases. Side effects of rasburicase are: allergic reactions, fever, nausea and vomiting. It should not be used in people with glucose-6-phosphate dehydrogenase deficiency because it can precipitate hemolytic anemia.

All cytostatics have **a teratogenic effect** on the embryo and fetus, so they should not be used during pregnancy, especially in the first trimester. They also **reduce male fertility** and shorten the reproductive life of women. However, no increased incidence of abortion or congenital anomalies has been observed in pregnancies that occur after the use of cytostatics.

Cardiotoxicity involves direct damage to myocardial cells by cytostatics. Not all cytostatics have a significant cardiotoxic effect, but some stand out in particular: anthracyclines (doxorubicin and daunorubicin). Toxic effects can be acute and chronic. Acute toxic effects occur after bolus injections of anthracyclines, and are manifested as supraventricular tachycardia, a decrease in the T-wave in the ECG, or the appearance of ventricular extrasystoles. Chronic toxic effects occur after a latent period of several months and are manifested as cardiomyopathy with heart failure. Cardiomyopathy is especially common if the patient has received more than 550 mg/m2 of anthracycline.

Myocardial damage that occurs after the use of anthracyclines is not reversible, and is based on damage to the mitochondria of cardiac muscle cells.

The cardiotoxicity of anthracycline preparations can be reduced in two ways. First, anthracyclines can be prepared as **liposomal** preparations, i.e. the drug molecules are coated with a lipid membrane that prevents contact with tissues that are not the target of therapy. It has been observed that the use of liposomal preparations of cytostatics generally carries less toxicity. Secondly, the drug **dexrazoxane** (a derivative of ethylenediaminetetraacetic acid, EDTA) can be given to the patient before and during the administration of anthracyclines, which prevents the oxidative and direct toxic effects of cytostatics on mitochondria. Dexrazoxane is given in a ratio of 10:1 with doxorubicin (e.g. 250 mg of dexrazoxane to 25 mg of doxorubicin).

Toxic effects on the urinary tract are characteristic of cisplatin, cyclophosphamide and ifosfamide. Cisplatin primarily damages the renal tubules, while cyclophosphamide and ifosfamide damage both the renal tubules and the bladder epithelium, causing **hemorrhagic cystitis**. Hemorrhagic cystitis is a consequence of the accumulation of acrolein, a metabolite of cyclophosphamide and ifosfamide, in the bladder. In addition, cyclophosphamide and ifosfamide lead to hyponatremia, because they increase water reabsorption in the collecting tubules of the kidneys.

The toxic effect of cisplatin can be reduced by good hydration of the patient with the use of mannitol, so that the flow of primary urine through the renal tubules is increased. An infusion of 2.5 L of physiological solution over 12 hours is recommended.

In addition, the simultaneous use of the thiol ester **amifostine**, which binds to free radicals (byproducts of the action of cytostatics) and neutralizes them, is useful.

The toxic effect of cyclophosphamide and ifosfamide on the bladder can be reduced by the simultaneous administration of **mesna**, a drug that binds specifically to acrolein and neutralizes it. Usually, the same amount of mesna is administered in units of weight as the cyclophosphamide was administered.

Liver damage can occur with numerous cytostatics, because they are either metabolized to toxic metabolites or are directly toxic to liver cells. Usually, the toxic effect is manifested by damage to hepatocytes (with a consequent increase in serum transaminases), but with the use of high doses of cytostatics, damage and obliteration of the small branches of the portal vein may occur, resulting in portal hypertension. The most pronounced hepatotoxic effects are caused by the following cytostatics: mercaptopurine, cyclophosphamide, asparaginase, plicamycin, nitrosoureas, methotrexate, busulfan, hydroxyurea.

Lung damage is primarily caused by the cytostatic **bleomycin**. It is concentrated in the lung tissue, because it has a small amount of the hydrolase enzyme, which breaks down bleomycin. Bleomycin has a direct toxic effect on type 1 pneumocytes and endothelial cells of the pulmonary capillaries. As a result of the action of bleomycin, pulmonary fibrosis gradually develops.

Damage to the skin and its adnexa is also caused by numerous cytostatics. Fluorouracil, doxorubicin, sunitinib and methotrexate can cause the **so-called hand-foot syndrome**, which is manifested by dry, red palms and soles that gradually become hyperpigmented. Hyperpigmentation in other areas of the skin can also be caused by busulfan, bleomycin, methotrexate, thiotepa, and fluorouracil. Taxanes and bleomycin can cause **nail loss**.

TOXICOLOGY

TREATMENT OF POISONED PERSON

The modern era is burdened by the existence of a large number of highly toxic substances that have been synthesized (or extracted from natural sources) due to the needs of increasingly developed technology. In addition, the production and consumption of drugs in the world is constantly growing, increasing the exposure of people (especially children) to toxic or potentially toxic substances. The consequence of this situation is a constant increase in the incidence of poisoning all over the world, including in our country. In the treatment of a poisoned person, initial therapy is of enormous (often crucial) importance, which often has to be undertaken at the site of poisoning or in the first health facility. The first step after encountering a poisoned person is not to establish an accurate diagnosis, i.e. identify the type of poison. This is most often not even possible, and would take up valuable time. Immediately after dealing with a poisoned person, the doctor should take general, non-specific measures that apply to any poisoning. First, the airway should be ensured, and then breathing and heart function should be ensured (by heart massage, artificial respiration). Then, an intravenous line should be provided and a urinary catheter should be introduced to monitor diuresis. All of the above procedures should not last more than 30 minutes. Of course, if the patient has been poisoned by gas or vapor, treatment should be started only after the poisoned person is taken out of the room in which he was.

Once basic physiological functions are ensured, the next priority is to prevent the absorption of the poison. If the poison has been spilled on the skin and clothing, then the clothing should be removed immediately and the skin should be washed with soap and water. If the poison has been swallowed (which is the most common case), vomiting should be induced or the stomach should be flushed. Both procedures are most effective if undertaken within one hour of ingestion, and are worth performing up to 4 hours after ingestion (up to 6 hours for opioids and anticholinergics, and up to 12 hours for salicylates, tricyclic antidepressants, and aminophylline).

Vomiting can only be induced if the patient is conscious and has not been poisoned by caustic agents, petroleum and its derivatives, or convulsive poisons. Vomiting is most easily induced with syrup of ipecac (see the chapter on emetics).

Gastric lavage is performed by inserting a nasogastric tube as wide as possible into the stomach, and then alternately introducing and eliminating warm water through the tube. The procedure is repeated until the water returning from the stomach becomes completely clear. If the patient is unconscious, gastric lavage can be performed only after the airway has been previously protected by inserting an endotracheal tube with cuff. Gastric lavage is contraindicated in patients poisoned by petroleum, proconvulsant poisons or caustic agents, as perforation of the esophagus or stomach with the tube may occur.

After removing the poison from the stomach, the patient should be given activated charcoal (1 g/kg body weight) dissolved in water to swallow or, if a tube is placed, a suspension of charcoal is poured through it. Activated charcoal is actually charcoal obtained by a special process activated by anaerobic combustion of animal remains (bones, ligaments, joint capsules). The activation process significantly increases the surface area of the charcoal particles, making them resemble a sponge. Poison molecules are absorbed onto such particles and are eliminated with feces.

In order to further accelerate the elimination of poison from the digestive tract, the patient should be given a laxative. Osmotic laxatives (70% sorbitol or MgSO4 - bitter salt) are most commonly used for this purpose. A lot of water should be given with the laxative to make the effect even more pronounced.

Only after all the previously mentioned measures have been taken, can the doctor devote more time to trying to find out which poison the patient has been poisoned with. First of all, statements from witnesses to the poisoning or the closest relatives should be taken into account; an insight into the place of poisoning (the medicine box, the poison packaging) can often indicate a solution. Physical examination of the poisoned person usually does not provide much information: a large number of poisonings have similar symptoms. However, some signs can be used:

1. Miosis can be caused by anticholinesterases and opioids;
2. Mydriasis is caused by anticholinergics, neuroleptics and tricyclic antidepressants;
3. Arsenic and phosphorus have a garlic-like odor; cyanides smell like bitter almonds; the rotting smell occurs after heavy metal poisoning.
4. Tachycardia is caused by anticholinergics, tricyclic antidepressants, cocaine, cyanides; bradycardia is caused by cardiotonic glycosides, beta-blockers, calcium channel blockers, and others.
5. Central cyanosis is caused by CO and substances that convert hemoglobin to methemoglobin (nitrites, for example). Pink skin color accompanies cyanide poisoning, which, by blocking tissue respiration, prevents the utilization of O2 from oxyhemoglobin.
6. Hypotension is caused by opioids, barbiturates, calcium channel blockers, neuroleptics, and antidepressants.

7. Hypertension is caused by cocaine, amphetamine, ergot alkaloids, naphazoline, and others.

When a poison acts specifically on certain receptors in the body, a poisoned person may develop groups of signs and symptoms that reflect the activation or blockade of these receptors in different organs. Such groups of signs and symptoms are called "**minor toxidromes**". "Minor" toxidromes are: **sympathomimetic** (due to activation of alpha and beta receptors of the sympathetic nervous system), **sympatholytic** (due to blockade of alpha and beta receptors), **cholinergic** (due to activation of muscarinic receptors), **parasympatholytic** (due to blockade of muscarinic receptors), **opioid** (due to activation of opioid receptors), **hallucinogenic and sedative**. If the poison is not so specific in its action that it acts only on certain receptors, but rather activates or blocks several different functional proteins on different types of cells, the damage will depend on the place of entry or exit from the body, or on the place of accumulation in the body, because at these places the poison is in the highest concentration, and therefore has the greatest harmful effect. The symptoms and signs that arise on this occasion correspond to the damage to the organs at the point of entry, exit or accumulation, and we speak of "**major toxidromes**". "Major" toxidromes are **hepatic** (signs and symptoms of liver damage), **renal** (signs and symptoms of kidney damage), **respiratory** (signs and symptoms of lung damage), **gastrointestinal and central** (signs and symptoms of brain damage).

If conditions exist, samples of vomit, stool, blood and urine should be sent to the National Poison Control Center (located at the VMA Toxicology Clinic in Belgrade). In any case, the aforementioned Center should be consulted by phone regarding further treatment of poisoned patients; its phone number is open 24 hours a day.

Further treatment of poisoned patients depends on the type of poison. In addition to symptomatic therapy to treat the consequences of the poison (for example, convulsions will be treated with sedatives, heart failure with cardiotonics), we can sometimes apply a drug that will neutralize the poison or its effect - an antidote.

The antidote for poisoning with morphine or other opioids is naloxone - a drug that binds to mi-receptors and blocks the effect of opioids. Benzodiazepine poisoning can also be treated with an antidote - a benzodiazepine receptor blocker flumazenil.

A special types of antidote are **chelates**. They got their name from the Greek word keli (cell), because with their nucleophilic radicals (groups with S, N or O) they capture and "lock" metal atoms, preventing their binding to tissues and facilitating their excretion through the kidneys. Chelates are used to treat metal and arsenic poisoning. The first chelate to come into use was **dimercaprol (dimercaptopropanol)**. Dimercaprol was first used to treat poisoning with the poison Lewisite, which contained arsenic. Later, it also proved very useful for treating acute poisoning with arsenic, mercury and lead. It has many side effects because it can bind to many cellular enzymes and thus inactivate them (vomiting, salivation, paresthesias, especially thrombocytopenia and decreased blood coagulability). A special problem is **hypertension** with tachycardia that dimercaprol can cause after sudden administration. Less toxic than dimercaprol is the thio-derivative of succinate: **succimer**. Succimer is indicated only for the treatment of children with blood lead concentrations greater than 450 micrograms/L; it is administered orally and effectively reduces blood lead levels, but it remains unclear whether it can also improve tissue damage that has already occurred. Side effects are limited to gastrointestinal disorders and increased transaminase levels (in about 8% of patients). **Calcium - disodium - ethylenediamine - tetraacetic acid (CaNa2-EDTA)** is a chelate with a special affinity for lead. It is used to treat lead poisoning. Since it also binds calcium to some extent, it can sometimes cause hypocalcemia and tetanic convulsions. In large doses, it is nephrotoxic.

Deferoxamine chelate is used to treat iron poisoning, and **penicillamine** chelate is used for copper poisoning (or for copper overload in Wilson's disease due to impaired bile excretion). Deferoxamine binds aluminum in addition to iron (e.g., in the case of aluminum accumulation in chronic renal failure). It is administered i.m. or i.v. It releases histamine (facial flushing, hypotension), stains urine dark red, and is **neurotoxic**. Penicillamine is also very toxic; like dimercaprol, it damages **the bone marrow and kidneys**. Since patients with Wilson's disease must receive this drug for life, periodic monitoring of blood counts and urine is necessary. A new chelate, **trientine**, which has a high affinity for copper and is considerably less toxic than penicillamine, is used only in patients who are intolerant to penicillamine.

For poisoning with organophosphorus insecticides and poisons, the antidotes are atropine (it blocks the muscarinic effects of the poison) and oximes (pralidoxime, obidoxime). The oximes regenerate acetylcholinesterases that have been phosphorylated and thus inactivated by the poisons. The effect of oximes is better the earlier they are applied after the moment of poisoning.

Table 36. Doses of some antidotes.

POISON	ANTIDOT	ROUTE OF ADMINISTRATION	DOSE	DOSE INTERVAL
Benzodiazepines	Flumazenil	i.v.	500 μg	One dose

Beta - blockers	Atropin	i.v.	0.3 mg	-
	Glucagon	i.v.	5 mg	-
Mercury, lead, arsenic	Dimercaprol	i.m.	2.5 mg/kg	6 h
Opioids	Naloxone	i.v.	0.4 mg	It could be repeated up to 10mg
Organophosphates	Atropin	i.v.	2 mg	30 min
	Pralidoxim	i.v.	1 g	-
Oral anticoagulants	Vitamin K1	i.m.	10 mg	24 h
Paracetamol	N-acetyl-cistein	i.v. infusion	150 mg/kg 15 min, then 50 mg/kg for 4 h and finally 100 mg/kg during 16 h	

Cyanide poisoning (or overdose of the antihypertensive sodium nitroprusside) is treated with several antidotes. **Hydroxycobalamin** (vitamin B12) directly binds the cyano group, thus preventing its binding to tissues. The administration of **Na-nitrite** converts hemoglobin into methemoglobin, which has a high affinity for the cyano group - it binds it and thus inactivates it. Finally, the poisoned person should receive **Na-thiosulfate** ($Na_2S_2O_3$), which supports the action of the rhodanase enzyme in erythrocytes; rhodanase converts the CN-group into non-toxic thiocyanate (CSN), which is excreted in the urine.

Finally, the poisoned person can be helped by accelerating the elimination of the poison from the body. This can be done in several ways:

a) **forced diuresis** - a decrease in the reabsorption of electrolytes and water in the distal tubules or Henle's loop leads to a decrease in the reabsorption of toxins from the primary urine. The result is an increase in the amount of urine and an increase in the amount of toxins eliminated. This effect is achieved by the use of strong loop diuretics, especially **furosemide**, with a large infusion of saline to maintain blood flow through the kidneys. An additional increase in the excretion of toxins can be achieved by the use of a base (NaHCO3) or an acid (NH_4Cl or vitamin C). By using a base, the urine becomes basic, so that toxins that are weak acids in the kidney tubules are completely dissociated; as such, they poorly pass the membrane of tubular cells, remain in the lumen and are excreted in the urine. Such forced diuresis is called **forced alkaline diuresis**. On the other hand, if the poison is a weak base, the urine should be acidified by the use of ammonium chloride. In acidic urine, the poison is more dissociated, which means that it is less reabsorbed and more excreted in the urine. This is **forced acid diuresis**.

b) **hemodialysis** - hemodialysis can remove poisons of lower molecular weight that bind little to plasma and tissue proteins in the body, whose volume of distribution is not too large, so that their concentration in the blood is relatively high. Hemodialysis is particularly effective in poisoning with lithium, salicylates, procainamide, ethyl and methyl alcohol and ethylene glycol. The effect is quite weak in poisoning with antidepressants and neuroleptics.

c) **hemoperfusion** - is the process of passing the patient's blood through tubes coated with activated charcoal. Poisons with large, polar molecules are absorbed onto the particles of this charcoal. Hemoperfusion is the method of choice for removing poisons in poisoning with methylxanthines (theophylline, caffeine), barbiturates (phenobarbitone), phenytoin, carbamazepine and salicylates. The condition for successful removal of poisons by hemoperfusion is that the substance in question has a volume of distribution that is not too large, so that its concentration in the blood is relatively high.

MANIFESTATIONS OF TOXICITY

Poisons, as well as drugs in supramaximal doses, bind to macromolecules of the cells of the human body, disrupting their functioning. If macromolecules of vital importance for the cell are blocked, the cell will die, either suddenly (necrosis) or gradually, through the process of apoptosis. Depending on the role of the dead cells in the organ to which they belong, poisoning will manifest itself in one way or another.

Damage to the liver by poison depends largely on whether the poison is metabolized in it or not. If the poison itself is not very biologically active, but is converted into toxic metabolites under the action of cytochrome P450, then the liver cells around the central vein of the lobule will suffer the most (because the activity of cytochrome P450 is highest in these cells). If the poison itself is active, the cells around the portal spaces will suffer the most, because they are exposed to the highest concentration of poison. If liver damage is not a direct result of the poison, but an allergic reaction to the poison or drug, areas with dead cells will be scattered throughout the liver.

When a poison acts on the kidney, the cells of the proximal tubules, which are exposed to the highest concentration of poison, suffer the most. Their function of reabsorption of important blood plasma components is lost, so glucose, amino acids, proteins and protein cylinders can be found in the urine.

Poisons often damage the human immune system, reducing its resistance to infections. All cytostatics and immunosuppressants have such an undesirable effect, so when they are used, the number of leukocytes in the patient's blood must be constantly monitored.

In the central nervous system, toxic manifestations are primarily caused by poisons that are liposoluble, and therefore easily pass through the blood-brain barrier (e.g. organic solvents, insecticides). The central nervous system reacts to poisons first with disturbances of consciousness (confusion, drowsiness, disorientation) and perception (illusions and hallucinations), and then with the appearance of convulsions.

Table 37. Drugs, and substances not used as drugs, with toxic effects on individual organs.

ORGAN	DRUGS	POISONS
Lungs	Bleomycine Amiodarone Busulphan	Sulphur dioxyde Nitrogen dyoxyde Ozone Paraquat Chlorine Berilium Phosgen ($CoCl_2$) Cadmium-oxyde
Kidneys	Cisplatine Cyclosporine A NSAIDs Aminoglycosides Vancomycin Iphosphamide Acyclovir	Citrinin (mycotoxin) Chlorophorm Mercury chloride
Liver	Paracetamol Ethanol Halotane Statins Isoniazide	Carbon-tetrachloride Berilium

GAS POISONING

Carbon monoxide (CO). It is formed during combustion in conditions without enough oxygen (closed rooms, garages). Its affinity for iron in hemoglobin is 200 times greater than its affinity for oxygen. It binds to hemoglobin and forms carboxyhemoglobin. Carboxyhemoglobin does not transport oxygen. The poisoned person first becomes confused, complains of a headache, and then falls into a soporous, and finally comatose state. Since the blood does not transport enough oxygen, central cyanosis occurs. The patient dies due to cardiac arrest and cessation of breathing. Treatment consists of removing the patient from the room with CO and then administering 100% oxygen via a mask. If there is a hyperbaric chamber, the patient can recover faster if exposed to pure oxygen under a pressure of two atmospheres. O2 displaces CO from its bond with hemoglobin.

Sulfur dioxide (SO2). Sulfur dioxide is an industrial gas that is produced by the combustion of fossil fuels, so poisoning is most common among workers in production. SO2 dissolves in the bronchial mucosa and, with water, forms sulfurous and sulfuric acids that damage the epithelium. A clinical picture similar to acute bronchitis with a spastic component develops. Poisoning is treated symptomatically, using bronchodilators, antibiotics and anti-inflammatory drugs.

Nitrogen dioxide (NO2) and ozone (O3) are gases that cause a number of industrial poisonings. Nitrogen dioxide poisoning most often occurs in workers who work with silage on agricultural land or in people who work near internal combustion engines. Unlike SO2, which damages the upper respiratory tract, NO2 and O3 cause damage to the alveoli and the smallest bronchioles. Toxic pulmonary edema occurs, often after a latent period of several hours (sometimes 48 hours). Treatment is symptomatic: administration of oxygen and corticosteroids.

HEAVY METALS POISONING

Poisoning with lead. Lead enters the human body most often through the gastrointestinal tract, in the form of inorganic and organic compounds. Poisonings of small children who put toys painted with lead-based paints in their mouths were especially common.

Lead can cause acute poisoning if ingested in large quantities at once. Acute poisoning can also occur from prolonged inhalation of gasoline vapors containing the organic lead compound: tetraethyl lead. Initially, **intestinal colic occurs**, followed by symptoms from the **CNS**: headache, insomnia, hallucinations, convulsions (in more severe poisonings, even coma).

Chronic lead poisoning is much more common and is characterized by the development of anemia, occasional colic-like abdominal pain (so-called lead colic), the appearance of a grayish border on the gums, symptoms from the nervous system (almost all symptoms can occur, and the most common are irritability, tremor, memory impairment and peripheral neuropathy) and, less often, interstitial nephritis.

Lead poisoning is treated with chelation, but only on condition that the patient has symptoms of poisoning; preventive use of chelation is contraindicated. Ca-Na2-EDTA (1 g i.v./12 hours for 3-5 days for adults, and 50 mg/kg/day i.v. in children) or dimercaprol (300-450 mg/m2/day i.m.) are used. In severe poisoning, these two chelates are used together.

Mercury poisoning. Elemental mercury is almost non-toxic because it is extremely poorly absorbed (for example, a folk remedy for ileus was mercury; the patient would drink about a hundred grams of mercury, which could sometimes, by its own weight, establish passage through the digestive tract). However, all mercury compounds, inorganic and organic, are toxic. These compounds are found in the wastewater of many industrial plants and accumulate in the tissues of some species of fish. In Japan, there have been several cases of mercury poisoning due to ingestion of the meat of such fish.

Acute mercury poisoning is primarily manifested by irritation of the gastrointestinal tract (vomiting, nausea, diarrhea), and soon damage to the renal tubules occurs.

Chronic poisoning is characterized by tubular damage to the kidneys, damage to the basal ganglia of the brain (impaired handwriting, irritability, personality disorders, ataxia, chorea, athetosis, tremor) and a mercury rim on the gingiva. The salivary glands are enlarged.

Mercury poisoning is treated with dimercaprol (3-5 mg/kg i.m./4 hours for 48 hours, then every 12 hours for 10 days) or succinate. Activated charcoal is not worth giving because it does not bind mercury.

Arsenic poisoning. Arsenic binds to the SH groups of many enzymes and structural proteins, inactivating them and leading to impaired function or death. Both elemental arsenic and its compounds (both inorganic and organic) are toxic. Large amounts of arsenic are released during coal combustion and ore smelting. Arsenic has also been used by criminals for centuries to poison humans and animals. Arsenic is most toxic when it is trivalent (e.g. in arsine gas: AsH3).

Arsenic is toxic to the nervous system, bone marrow, liver, respiratory tract, skin, and kidneys.

Inorganic arsenic compounds ingested in large quantities cause acute poisoning: severe gastroenteritis, laryngotracheobronchitis, and shock occur. If an acute attack is survived, bone marrow depression, encephalopathy, and peripheral sensory neuropathy develop. The patient smells of garlic.

Organic arsenic compounds cause encephalopathy only when ingested acutely.

A special form of acute arsenic poisoning is poisoning with arsine gas (AsH3). Acute hemolysis dominates here because arsine binds to hemoglobin and oxidizes, turning into a hemolytic agent. Due to the sudden hemolysis, a large amount of hemoglobin is found in the plasma, is filtered in the glomeruli and clogs the renal tubules. The result is acute renal failure.

Chronic poisoning gives a characteristic clinical picture: the skin becomes hyperkeratotic (especially on the palms and soles), hyperpigmented, the hair falls out and the nails acquire whitish lines (Mi's lines). Bone marrow depression results in anemia and pallor that is locally interspersed with pale to red spots (due to vasodilation): the so-called **milk and rose** complexion. The patient is cachectic, suffers from sensory neuropathy, conjunctivitis and loss of renal function.

Arsenic poisoning is treated with dimercaprol (3-5 mg/kg i.m. every 4 hours for the first 48 hours, then every 12 hours for 10 days).

Beryllium poisoning. Beryllium is used in alloys for the manufacture of electrical equipment. In the body, it binds most strongly to enzymes that use magnesium as a cofactor, inhibiting them. If inhaled, beryllium causes acute pneumonitis accompanied by pulmonary edema. Symptoms usually appear after a latency period of several days. With prolonged inhalation of small amounts of beryllium, chronic poisoning occurs, characterized by the appearance of granulomas in the lungs. Over time, respiratory failure develops, and patients are at increased risk of developing lung cancer.

If beryllium comes into contact with the skin, acute dermatitis develops, with redness and blistering.

In acute beryllium poisoning, Ca-Na2-EDTA, corticosteroids, and antibiotics should be administered.

HYDROCARBONS POISONING

Hydrocarbons can be classified into three large groups from a toxicological point of view: aliphatic hydrocarbons with straight and branched chains, aromatic and halogenated hydrocarbons.

Aliphatic hydrocarbons make up the majority of petroleum distillates: gasoline, kerosene and solvents. Petroleum distillates are significantly more toxic if inhaled than if swallowed. For example, if a patient swallows 1 liter of gasoline, they will fare better than if they had aspirated 1 milliliter! When inhaled, these substances cause severe bronchopneumonia and pulmonary edema. Therefore, it is of the utmost importance when treating patients who have swallowed petroleum distillates to avoid aspiration during gastric lavage.

Aliphatic hydrocarbons in acute oral poisoning cause nausea, penetrate the central nervous system due to liposolubility, and lead to loss of consciousness and convulsions. They sensitize the myocardium to the effects of catecholamines, which creates conditions for the development of arrhythmias. In chronic poisoning, the picture of polyneuropathy dominates. Treatment of aliphatic hydrocarbon poisoning is only symptomatic.

Aromatic hydrocarbons have a cyclic molecular structure. Of these, benzene, xylene and toluene are most commonly used as solvents in rubber and plastic adhesives. The lethal dose of these substances is 2-5 g/kg of body weight, if ingested by inhalation or parenterally. After acute poisoning by inhalation or ingestion, they penetrate the central nervous system, and first euphoria occurs, then nausea, blurred vision, tremors, loss of consciousness and convulsions. Arrhythmias can occur due to myocardial sensitization to catecholamines. Treatment is symptomatic, but it should be remembered that the use of sympathomimetic drugs is contraindicated.

When these substances are ingested chronically (most often this happens when inhaling glue vapors due to the euphoria-inducing effect), they lead to bone marrow depression (sometimes leukemia) and irreversible damage to the **cerebellum**, with the appearance of ataxia, tremors and emotional lability.

Halogenated hydrocarbons (carbon tetrachloride, trichloroethylene, chloroform, and others) are mainly used as organic solvents and in cleaning agents. The lethal dose of these substances is only 3-5 ml after oral ingestion or inhalation. Since they are liposoluble, they penetrate the central nervous system, causing confusion, loss of consciousness, and convulsions. They are characteristically damaging to the **liver and kidneys**, often after a latent period of several days. They cause centrilobular necrosis in the liver, as they are transformed under the action of cytochrome P450 to even more toxic metabolites. They also sensitize the myocardium to catecholamines, thereby increasing the tendency to develop arrhythmias. With chronic ingestion, these substances lead to encephalopathy, with the following symptoms: memory loss, fatigue, tremor, blurred vision, and loss of peripheral color vision.

When halogenated hydrocarbons burn in a confined space (e.g. in a fire), they decompose to phosgene ($CoCl_2$), a highly toxic gas that causes acute pulmonary edema.

There is no specific treatment.

INSECTICIDE POISONING

According to their chemical structure, insecticides are divided into three large groups: organic chlorine compounds, cholinesterase inhibitors and insecticides of plant origin.

a) ***Poisoning with organochlorine insecticides*** (dichlorodiphenyl trichloroethane-DDT, lindane, aldrin and others) is characterized by CNS stimulation. These substances prevent the inactivation of Na^+ channels in the neuronal membrane and lead to tremors and convulsions. They also sensitize the myocardium to the pro-arrhythmogenic effect of catecholamines. There is no specific antidote.

b) ***Poisoning with cholinesterase inhibitors*** (see the chapter on the autonomic nervous system).

c) ***Poisoning with plant insecticides***. Plant insecticides (**rotenone, pyrethrins, nicotine**) are sufficiently liposoluble to penetrate the CNS. They cause CNS stimulation, manifested by tremors, hallucinations and convulsions. There is no specific antidote, but poisoning is treated symptomatically with anticonvulsants and sedatives. In addition to its effects on the CNS, rotenone irritates the mucous membrane of the digestive and respiratory tract, and nicotine causes hypertension, arrhythmia and neuromuscular blockade of the depolarization type (nicotine normally activates receptors on the neuromuscular junction and leads to membrane depolarization: Ca^{++} channels open, Ca^{++} enters the cells and contraction occurs, Ca^{++} channels are then spontaneously inactivated, Ca^{++} entry decreases and the cells relax. However, since nicotine remains bound to the receptors, the membrane remains depolarized and a new contraction cannot occur: muscle paralysis occurs).

Since nicotine is metabolized quickly, if the patient survives the first 4 hours of poisoning, the prognosis is good.

HERBICIDE POISONING

Two types of herbicides are most commonly used today: chlorophenoxy compounds and bipyridyls.

Chlorphenoxy compounds (2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid) disrupt the process of oxidative phosphorylation and damage cell membranes. They depress the CNS and lead to coma accompanied by extreme muscle hypotension. Blood pressure drops and remains low for a long time. Liver and kidney damage is manifested in those who survive the coma phase.

Long-term exposure to these compounds increases the risk of Hodgkin lymphoma or soft tissue sarcoma.

Tetrachlorodibenzo-p-dioxin (TCDD, dioxin) is often found with chlorophenoxy compounds as a breakdown product or impurity formed during the production process. Dioxin causes acne on the skin, muscle pain that increases with physical activity, insomnia, emotional lability, irritability and loss of libido for several days after being ingested. Animal experiments have shown its strong mutagenic effect.

Of the ***bipyridyls, paraquat*** is the most widely used herbicide. In the lungs, it inhibits the enzyme superoxide dismutase, which makes the lung parenchyma particularly sensitive to the toxic effects of oxygen. It is also converted into a reduced monocationic form, which is then reoxidized and, in the presence of oxygen, produces superoxide anion, which damages pneumocytes. After oral ingestion, irritation of the digestive tract (bleeding, pain) immediately occurs. The condition may begin to improve, but after a few days, pulmonary edema develops, which progresses to pulmonary fibrosis. Myocardium and liver damage also occur. Paraquat is an extremely toxic substance, as the lethal dose for humans after oral ingestion is only 4 mg/kg.

Treatment of poisoning is only symptomatic.

RODENTICIDE POISONING

Fluoroacetate is metabolized to fluorotricarboxylic acid, which inhibits the Krebs cycle. It is toxic to all tissues. In acute poisoning, signs of CNS irritation (vomiting, excitability, convulsions) occur, followed by coma with respiratory depression. In addition, pulmonary edema occurs. Poisoning is treated with glyceryl monoacetate (0.5 ml/kg i.v.) or ethyl alcohol (0.5 ml/kg of a 10% solution). Due to its extreme toxicity (lethal dose is 50-100 mg), fluoroacetate is no longer used as a rodenticide.

Thallium has been widely used as a rat and ant poison. There is usually a latency period of several days between ingestion and the appearance of the first symptoms. Signs of damage to the peripheral (ptosis, paresthesias, pain in the extremities) and central (tremor, confused speech, choreiform movements, convulsions) nervous system appear. Hair falls out, the skin atrophies, and a blue rim appears on the gums. Death occurs due to pulmonary edema and/or anuria. In addition to symptomatic therapy, oral Prussian blue (K-ferri-hexacyanoferrate) is administered, which binds thallium and prevents its absorption from the intestine.

Preparations made from the plant Scylla maritima, which are rich in cardiotonic glycosides, are also used as rodenticides. Poisoning with such preparations resembles an overdose of cardiotonic glycosides.

Also, anticoagulant substances are used in rat poisons. Ingestion of such a poison is manifested by bleeding, and the patient can be helped by administering vitamin K.

CYANIDE POISONING

Compounds containing the cyano group (CN) are released in large quantities during industrial metal processing; the pits of stone fruits (e.g. apricots, apples, cherries, peaches, plums) contain glycosides that release hydrogen cyanide in the intestines. The cyano group inhibits cytochrome oxidase, i.e., interrupts cellular respiration. Immediately after ingestion, the patient breathes rapidly, blood pressure drops, and then convulsions and coma occur. The skin is characteristically red, and the doctor can smell the smell of bitter almonds, which comes from the patient.

Poisoning is treated with antidotes: nitrites, hydroxycobalamin and thiosulfate. **Sodium nitrite** is administered intravenously, as a 3% solution, at a rate of 2.5-5 ml/min. The initial dose of this drug is 0.39 ml/kg, provided that the patient has a normal hemoglobin level (140 g/l). It converts hemoglobin into methemoglobin, which then binds cyanide.

Sodium thiosulfate is also administered intravenously, as a 25% solution, at a rate of 2.5-5ml. The initial dose of this drug is 1.95 ml/kg, provided that the patient has a normal hemoglobin level (140 g/l). Thiosulfate converts cyanide into thiocyanate, which is non-toxic.

Finally, the patient should also be given **hydroxycobalamin**, which binds cyanide and is converted into non-toxic cyanocobalamin. The dose is 50 mg/kg.

ETHYL ALCOHOL

Ethyl alcohol (ethanol) is found in various beverages that are obtained by fermentation and then distillation of plant-based materials with many complex and simple sugars. The strength of alcoholic beverages is expressed in volume percentages (v%), which indicate how many milliliters of pure alcohol are in 100ml of the beverage. Thus, beer has 3 - 4 v%, wine about 10 v%, and "strong" drinks about 40 v% of pure ethanol. Ethyl alcohol first leads to excitation (due to the removal of cortical control, the alcohol drinker loses moral norms of behavior) and then to CNS inhibition (drowsiness, motor incoordination, in higher doses sleep and coma). It also causes hypoglycemia and hypothermia. The mechanism of action of alcohol has not yet been established with certainty. The lethal dose for an adult is 400 ml of pure ethanol, which is about 1L of "hard" liquor.

Alcohol is metabolized in the liver by alcohol dehydrogenase. It is first converted to **acetaldehyde and then to acetic acid**. **Disulfiram** prevents the transformation of acetaldehyde into acetic acid, thus leading to the accumulation of acetaldehyde. Acetaldehyde is toxic and causes nausea, vomiting, and flushing of the upper body. Disulfiram is sometimes given to patients being treated for alcoholism to prevent them from drinking alcohol again; if the patient drinks a glass of alcohol while on disulfiram therapy, they will experience the side effects mentioned above. There is also a substance that inhibits the formation of acetylaldehyde from ethanol: **4-methylpyrazole (fomepizole)**. The liver's capacity to metabolize alcohol is very limited and is completely saturated after consuming a small amount of alcohol. Regardless of the amount ingested, the same amount of alcohol is always metabolized per unit of time - as much as the liver can break down. This type of metabolism that occurs after the elimination mechanism is saturated is called zero-order metabolism. An adult can break down an average of 7-10g of pure alcohol in one hour. Alcohol poisoning is treated primarily symptomatically. The vital functions of the poisoned person should be maintained (artificial or assisted respiration, fluid infusions to maintain kidney function, general care) until the liver eliminates the alcohol and the depressive effect on the CNS subsides. The administration of 5% glucose is desirable, because hypoglycemia often develops in poisoned people; In addition to glucose, **vitamin B1 (thiamine),** 100 mg intramuscularly, should be given to avoid the formation of lactic acid. In the most severe poisonings, ethyl alcohol can be successfully eliminated by hemodialysis.

The concentration of alcohol in the blood can be measured and thus the degree of poisoning can be assessed. A concentration below 150 mg/dl indicates moderate, between 150 and 300 mg/dl moderate and above 300 mg/dl severe poisoning. A concentration of 400 mg/dl or more is often fatal.

METHYL ALCOHOL (METHANOL) POISONING

Methanol (CH_3OH) is found in large quantities in low-quality alcoholic beverages. It is used in industry as an organic solvent or propellant. Methanol, like ethyl alcohol, causes CNS depression. However, the metabolism of methanol (in the liver, under the action of alcohol dehydrogenase) first produces formaldehyde, and then the extremely toxic formic acid ($HCOOH$). Formic acid causes acidosis and has a neurotoxic effect: **blindness**, convulsions and severe headache occur. Blindness is preceded by visual impairment, which patients describe as a "snowstorm" experience. It is believed that formaldehyde is responsible for the specific toxic effect on the retina.

Methanol is metabolized and excreted five times slower than ethanol. The lethal dose of methanol after oral administration is 60-250ml.

Methanol poisoning is treated with ethanol. Ethanol occupies alcohol dehydrogenase and prevents the metabolism of methanol to formic acid. 50% ethanol is administered orally, in a dose of 1.5 ml/kg initially, then every two hours by 0.5-1 ml/kg, for 4 days. The level of ethanol in the blood should be 100 - 150 mg/dl.

4-methylpyrazole (fomepizole) can be used instead of ethanol. It inhibits alcohol dehydrogenase and prevents the conversion of methanol to formaldehyde. The initial dose of fomepizole is 15 mg/kg intravenously, in a slow infusion; the same or slightly lower dose can be repeated every 12 hours. The drug can cause headache and hypotension.

In the most severe poisonings, hemodialysis should be used, which successfully removes methanol and formic acid. The presence of acidosis is treated with intravenous administration of sodium bicarbonate.

ETHYLENE GLYCOL POISONING

Ethylene glycol is used as an organic solvent and as an antifreeze. After oral ingestion, it causes irritation of the gastrointestinal tract and CNS depression (similar to ethyl alcohol). As it is metabolized in the liver under the action of alcohol dehydrogenase (it is converted into oxalic acid), CNS depression is corrected after a certain time and the patient enters the so-called **latent phase**. In the meantime, oxalate accumulates in the body, binds Ca++ from the serum and provokes symptoms of tetany due to **hypocalcemia**. In addition to oxalate, ethylene glycol esters and ethers are formed, which also have a toxic effect on the brain and other organs. **Hypoglycemia** also occurs. **The third phase of poisoning is damage to the kidney tubules** due to the deposition of calcium oxalate, which can also end in acute renal failure.

The lethal dose of ethylene glycol is about 100g.

Treatment of ethylene glycol poisoning includes the administration of **ethyl alcohol** (to reduce the metabolism of ethylene glycol to oxalate) or **4-methylpyrazole (fomepizole),** and in severe cases, hemodialysis. The dosage of ethanol and fomepizole is the same as for methanol poisoning. Hypocalcemia can be controlled by intravenous administration of calcium gluconate (10ml of a 10% solution), and hypoglycemia by infusion of 5% glucose.

POISONING WITH MUSHROOMS

There are about 2,500 species of mushrooms growing in Europe, of which about 30 species are poisonous in our country, and 7 of them cause fatal poisoning. Mushroom poisoning is called **mycetism** (from the Greek word myces, meaning fungus). The most practical division of mushroom poisoning is into those with short and those with long latency, i.e. according to whether the time period between the consumption of mushrooms and the appearance of the first symptoms is short or long.

Mushroom poisoning with short latency

A large number of mushrooms cause poisoning with short latency; depending on the mechanism of action of the toxin, there are several syndromes that they can cause:

a) **gastroenterocolitis**, followed after a latency of several hours by nausea, vomiting, abdominal pain and diarrhea; it is caused by the lead miner (Entoloma lividum), the spittlebug (Russulla emetica), the madman (Boletus satanas), the stinkbug (Russulla foetens) and others. The treatment is rehydration with intravenous solutions.

b) **Antabuse syndrome**, which consists of symptoms similar to those of simultaneous use of alcohol and disulfiram (redness of the neck and face, tachycardia, headache, feeling of suffocation); it is caused by the large pus mushroom (Coprinus comatus), if alcoholic beverages are consumed with it.

c) **Pantherin syndrome**, which resembles atropine poisoning; it is caused by the panther mushroom (Amanita pantherina). This poisoning is treated only with general measures.

d) **Muscarinic syndrome**, which occurs due to the action of the toxin muscarine, which binds to muscarinic receptors and activates them; the poisoned person feels warmth in the skin (due to vasodilation), his vision becomes blurred (due to spasm of accommodation and miosis), bradycardia occurs (due to direct action on muscarinic receptors in the heart) and hypersalivation. This syndrome is caused by mushrooms from the genera Inocybe and Clitocybe, but also fly agarics (Amanita muscaria, a bright red mushroom cap with white dots); fly agarics are about 100 times less poisonous than Inocybe and Clitocybe. Muscarinic syndrome can be successfully treated with atropine.

Mushroom poisoning with long latency

a) In our country, the most significant causative agents of this type of poisoning are the **„death cap“ (green death cap – Amanita phalloides, white death cap – Amanita verna)**. These mushrooms contain the cyclic polypeptides amanitin and phalloidin, which are resistant to the action of digestive enzymes, are absorbed and cause liver cell death and submucosal bleeding in the gastrointestinal tract. Amanitin is far more toxic, as it inhibits RNA polymerase, while phalloidin interferes with the functioning of the cell membrane and prevents actin polymerization. Clinical picture of poisoning: about 15 hours after consuming these mushrooms, enterocolitis occurs, which spontaneously resolves within 2 days. Then the patient's condition temporarily improves, only to suddenly deteriorate after 7-10 days, with hepatitis accompanied by jaundice. In more severe poisonings, this sequence of events can be even faster, and hepatitis is accompanied by kidney and heart failure. Fatal outcome occurs in 30-50% of poisoned adults and almost 100% of poisoned children. There is still no effective antidote for this poisoning, so treatment is

limited to general measures. Poisoned persons are given very large doses of penicillin G intravenously (1,000,000 IU per kilogram of body weight), because it partially prevents the poison from entering hepatocytes and binding to RNA polymerase. The poison can be partially removed from the blood by hemoperfusion. Since amanitin is subject to enterohepatic recirculation, it is worth giving the patient activated charcoal orally on several occasions, so that as much of the poison as possible is bound and excreted in the stool. The use of silymarin in the treatment of this poisoning is controversial. Silymarin is an extract obtained from the plant Silybum marianum (popular name: viper's grass), and contains about 50% silybin, while the rest is silychristin and silydianin. These compounds are polyphenolic flavonoids, which act primarily as antioxidants, and then stimulate the expression of RNA polymerase in hepatocytes and have an inflammatory effect. Silymarin or purified silybin is used not only to treat poisoning with Amanita phalloides, but also to treat poisoning with other hepatotoxic substances, such as carbon tetrachloride, ethanol, paracetamol, halothane or erythromycin estolate. Silymarin is administered intravenously, at a dose of about 100 milligrams per kilogram of body weight.

b) **Rhabdomyolysis** syndrome occurs 24 to 72 hours after ingestion of the mushroom **Tricholoma equestre**. This syndrome is particularly common in people who eat the aforementioned mushroom and are otherwise on chronic statin therapy. The mechanism of the toxic effect is not yet clear. The poisoned person experiences nausea (not vomiting), muscle weakness and sweating. Serum creatine kinase is greatly elevated, as are the liver enzymes alanine and aspartate aminotransferase. Severe myocarditis then develops, leading to acute heart failure. Rhabdomyolysis releases large amounts of myoglobin into the blood, which can block the renal tubules and cause acute renal failure. The mortality rate is about 20%. There is no specific antidote for this poisoning.

c) **A syndrome resembling paraquat poisoning** occurs if mushrooms of the genus **Cortinarius** are eaten. They contain a substance orellanine, similar to paraquat in chemical structure, which is transformed by cytochromes into a toxic metabolite (ortho-semiquinone) and leads to the formation of free radicals. Nonspecific symptoms begin 24 to 36 hours after ingestion of the mushrooms (nausea, abdominal and lumbar pain, polydipsia), and after about 8 days, interstitial nephritis occurs, which is often complicated by acute renal failure. As many as 50% of poisoned people progress from acute to chronic renal failure. Treatment of this poisoning is symptomatic.

d) **Renal failure syndrome** occurs after ingestion of the mushroom **Amanita smithiana**, which is mainly found in the northwestern part of the United States. These mushrooms are mainly poisoned by people looking for the so-called Matsutake are edible mushrooms that closely resemble Amanita smithiana. These mushrooms produce the toxin allelic norleucine (aminohexadienoic acid) that selectively affects renal tubular cells and causes their necrosis. Mild gastrointestinal symptoms occur within a few hours of ingestion, which soon resolve, followed by acute renal failure 3 to 6 days later. Kidney biopsies performed a few weeks after poisoning show signs of interstitial fibrosis and tubular necrosis. Patients are maintained on hemodialysis, and after a month or two, renal function generally improves to the point where dialysis is no longer necessary.

SNAKE BITE

A venomous snake bite causes snake venom poisoning, which is called ophidism ("ofis" in Greek means snake). There are about 370 species of venomous snakes in the world, of which only two are found in Serbia: the viper (Vipera ammodytes) and the common viper (Vipera berus). The viper is about 80 cm long, has a heart-shaped head with a small horn on the nose, a lyre-shaped pattern on the head and a zigzag pattern on the back. It is not timid, it likes rocky terrain. The common viper is about 75 cm long, has a wider and rounder head than the viper. It has a white stripe along the edge of its upper jaw, its eye is large, with a red reflection, and on its crown there are three large horny plates.

The venom of snakes is located in modified salivary glands behind the eye, which are connected by an excretory duct to two hollow teeth on the top of the upper jaw (about 5-7 mm long). When a snake bites a person, the venom from the glands is injected through these two teeth into the subcutaneous tissue. The venom contains the enzymes protease, phospholipase, oxidase, hyaluronidase, as well as factors that affect the blood clotting process.

Pain, swelling, blue skin color, and subcutaneous hemorrhages occur at the site of the bite. Hypotension occurs, and sometimes a state of shock. Due to impaired blood coagulation, bleeding occurs from the gums, uterus, conjunctiva, large intestine, or stomach. If shock develops, anuria and acute renal failure may occur. The severity of the clinical picture depends on the amount of venom injected and the body weight of the person bitten. Children under 5 years of age are most at risk.

The person bitten should be immediately made to lie still, and the limb where the bite occurred should be **immobilized** with a splint. The wounds from the snake's teeth should be washed with water and connected with a 5mm deep incision. Then the venom should be sucked out with the mouth or a rubber pump (up to 30% of the venom can be removed in this way). Place tourniquets with a rubber hose or tape above and below the bite, and tighten them so that they obstruct lymph drainage, but not

arterial and venous blood flow. Move the tourniquets every 20 minutes, as the swelling spreads. Transport the patient to the hospital as soon as possible.

As soon as possible (no later than within 4 hours), the patient should receive **anti-snake serum**, which is obtained by immunizing horses with snake venom. Before administering the serum, it should be checked whether the patient is allergic to it. This is done by intradermally injecting 0.02 ml of diluted serum with saline in a ratio of 1:100, and observing for 10 minutes. It is also necessary to inject normal saline intradermally as a control. If swelling with redness does not occur, the serum can then be given to the patient.

The serum is given by intravenous infusion, diluted with saline. At least 3 ampoules of serum of 3000IJ each should be given. In addition to the anti-viper serum, the patient should be given antibiotics and anti-tetanus serum. Coagulation disorders should also be corrected and circulatory shock should be combated.

About 30% of patients develop serum sickness after serum administration.

DESENSITIZATION

If the patient is hypersensitive to horse serum, it must still be administered, because the bite is life-threatening. In that case, before administering the serum, we perform a desensitization procedure. The serum is diluted with physiological saline in a ratio of 1:100, and 0.05 ml is injected subcutaneously. Then, double the amount every 5 minutes until 1 ml of serum diluted in a ratio of 1:10 is used. If there is no reaction then, dilute the entire amount of serum in a ratio of 1:50, and administer it by slow intravenous infusion, drop by drop. Have all the necessary medications with you to combat an anaphylactic reaction: adrenaline, corticosteroids, antihistamine.

POISONING WITH ACIDS AND BASES

If strong acids or bases are swallowed, they cause the death (necrosis) of all structures they come into contact with. Necrosis occurs primarily on and around the lips, in the oral cavity, and in the esophagus. Acids cause so-called coagulation necrosis, which is rigid and retains the shape of the damaged organ. Bases cause colliquation necrosis, in which the affected tissue turns into a mushy mass. In acid and base poisoning, the patient suffers severe pain and is usually in a state of cardiovascular collapse. Vomiting should never be induced in such patients, nor should their stomachs be lavaged! Both interventions will result in perforation of the esophagus, which directly results in mediastinitis with a fatal outcome. The patient should initially be given only water or milk to drink (a few liters) to dilute the ingested acid or base (but only if the poisoned person was found immediately after ingesting the poison). The opioid analgesic morphine should also be given to control the pain. The poisoned person should then be hospitalized, and cardiovascular collapse should be controlled with infusions, and the infection with antibiotics.

The patient should not take any food for several weeks, until the wounds in the oral cavity and on the esophagus heal. Then a long and persistent fight with esophageal stenosis due to fibrosis will begin, which is treated with the use of corticosteroids and dilation of the esophagus using metal rods. In the meantime, the patient is fed parenterally.

Bases usually cause deeper necrosis than acids, but in acid poisoning, an additional complication may occur in a small number of patients: **acute renal failure**. During coagulation of esophageal tissue, abnormal proteins of lower molecular weight are sometimes formed, which penetrate the blood, reach the kidneys and there, after filtration in the glomerulus, clog the tubules. This should be taken into account, and the first appearance of a decrease in diuresis in poisoned patients should be responded to by administering high doses of loop diuretics and increasing the infusion of crystalloid solutions.

ЛИТЕРАТУРА

Adeyinka A, Layer DA. Neuromuscular Blocking Agents. [Updated 2024 Jun 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Ahn CH, Choi SH. New Drugs for Treating Dyslipidemia: Beyond Statins. Diabetes & Metabolism Journal 2015; 39(2): 87-94.

Akel M, Patel P, Parmar M. Abaloparatide. [Updated 2024 Jan 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Anonymous. Rasburicase. Aust Prescr 2003; 26:70.

Anonymous. Bosentan. Aust Prescr 2003; 26:69.

Arsenijević S. Organska hemija. 4. izd., Zavod za udžbenike i nastavna sredstva, Beograd, 1978: 477 str.

Aschenbrenner DS, Venable SJ. Drug Therapy in Nursing, Fourth Edition, Lippincott Williams & Wilkins, 2012.

Azevedo VF, Kos IA, Vargas-Santos AB, da Rocha Castelar Pinheiro G, Dos Santos Paiva E. Benzbromarone in the treatment of gout. Adv Rheumatol. 2019;59(1):37.

Babalska ZŁ, Korbecka-Paczkowska M, Karpiński TM. Wound Antiseptics and European Guidelines for Antiseptic Application in Wound Treatment. Pharmaceuticals (Basel). 2021;14(12):1253.

Bajwa SJS, Vinayagam S, Shinde S, Dalal S, Vennel J, Nanda S. Recent advancements in total intravenous anaesthesia and anaesthetic pharmacology. Indian J Anaesth. 2023;67(1):56-62.

Baskaran AB, Grebenciucova E, Shoemaker T, Graham EL. Current Updates on the Diagnosis and Management of Multiple Sclerosis for the General Neurologist. J Clin Neurol. 2023;19(3):217-229.

Behrman RE, Kliegman RM, Arvin AM. Nelson Textbook of Pediatrics. 15th ed., WB Saunders Co, Philadelphia, 1996: pp 2200.

Bennet JC, Plum F. Cecil Texbook of Medicine. 21th ed., WB Saunders Co, Philadelphia, 1999.

Benet LZ, Galeazzi RL. Noncompartmental determination of the steady-state volume of distribution. J Pharm Sci 1979; 68: 1971-1974.

Benson RC. Priručnik iz akušerstva i ginekologije. 2. izd., Savre-mena Administracija, Beograd, 1989: 939 str.

Benzodiazepines, reviewing long term use: a suggested approach. Prescribing Practice Review. National Prescribing Service Ltd., No. 4 July 1999. Dostupno na: http://www.nps.org.au/data/assets/ pdf_file/0004/16915/ppr04.pdf, poslednji put posecena veb stranica 3.7.2013.

Bev-Lorraine T, Dreisbach RH. Trovanja, priručnik. 13. Izdanje, Data Status, Beograd, 2005.

Богдановић С. Фармакологија. 1 издање, Научна Књига, Београд, 1967: 830 str.

Bor S, Kalkan İH, Savarino E, et al. Prokinetics-safety and efficacy: The European Society of Neurogastroenterology and Motility/The American Neurogastroenterology and Motility Society expert review. Neurogastroenterol Motil. 2024;36(5):e14774

Bousquet P, Hudson A, García-Sevilla JA, Li JX. Imidazoline Receptor System: The Past, the Present, and the Future. Pharmacol Rev. 2020;72(1):50-79.

Brayfield A. Martindale The Complete Drug Reference. 38th ed., The Pharmaceutical Press, London, 2014.

British National Formulary. No 35, British Medical Association and Royal Pharmaceutical Society of Great Britain, London, 1998: 736 str.

Brunton LL, Chabner B, Knollman B. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed., McGraw - Hill, New York, 2010.

Calderon-Ospina CA, Nava-Mesa MO, Paez-Hurtado AM. Update on Safety Profiles of Vitamins B1, B6, and B12: A Narrative Review. Ther Clin Risk Manag. 2020;16:1275-1288.

Capizzi RL: Recent developments and emerging options: The role of amifostine as a broad-spectrum cytoprotective agent. Semin Oncol 26 (suppl 7):1-2, 1999.

Carazo A, Macáková K, Matoušová K, Krčmová LK, Protti M, Mladěnka P. Vitamin A Update: Forms, Sources, Kinetics, Detection, Function, Deficiency, Therapeutic Use and Toxicity. Nutrients. 2021;13(5):1703.

Cerillo JL, Parmar M. Tofersen. 2023 Nov 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–.

Chen EQ, Tang H. The current status of combination therapy of Chronic Hepatitis B. Eur Rev Med Pharmacol Sci 2013; 17(15): 2023-31.

Chey WD, Howden CW, Moss SF, Morgan DR, et al. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. The American Journal of Gastroenterology 2024;119(9):1730-1753.

Cooper JS, Phuyal P, Shah N. Oxygen Toxicity. 2020 Nov 19. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 28613494.

Craig CR, Stitzel RE. Modern Pharmacology with Clinical Appli-cations. 6th edition, Lippincott Williams & Wilkins, 2004.

Добутамин. Сажетак карактеристика лека. Hameln pharma-ceuticals, ltd. Electronic medicines compendium., 2020, Dostupno na: http://www.medicines.org.uk/emc/medicine/20891/ spc#PHARMACODYNAMIC_PROPS

Doogue MP, Polasek TM. Drug dosing in renal disease. Clin Biochem Rev 2011; 32(2): 69-73.

Duggan S. Vosoritide: First Approval. Drugs. 2021;81(17):2057-2062.

Edwards M, Can AS. Progestins. [Updated 2024 Jan 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-

Farès M, Liotier J, Mathevon T, Pic D, Perrier C, Schmidt J. Usefulness of Nefopam in Treating Pain of Severe Uncomplicated Renal Colics in Adults Admitted to Emergency Units**:** A Randomised Double-Blind Controlled Trial. The 'INCoNU' Study. Emerg Med J 2013; 30(2): 143-148.

Feng Y, He X, Yang Y, Chao D, Lazarus LH, Xia Y. Current research on opioid receptor function. Curr Drug Targets 2012; 13(2): 230-46.

Fong IW. New Cephalosporins: fifth and sixth generations. In: New Antimicrobials: For the Present and the Future. Cham: Springer International Publishing, 2023. p. 25-38.

Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: A Systematic Update. Int J Mol Sci. 2022;23(23):14631.

Ghofrani HA, Humbert M, Langleben D, Schermuly R, Stasch JP, Wilkins MR, Klinger JR, Riociguat: Mode of action and clinical development in pulmonary hypertension, CHEST (2016), doi: 10.1016/j.chest.2016.05.024.

Gilbert DN, Chanbers HF, Saag MS et al. The Sanford Guide to Antimicrobial Therapy. 54th ed., Antimicrobial Therapy Inc, Sperryville, USA, 2024.

Godier A, Martin AC. Specific Antidotes for Direct Oral Anticoagulant Reversal: Case Closed or Cold Case? Circulation. 2019;140(18):1445-1447.

Gonzalez LE, Boylan PM. Netarsudil for the Treatment of Open-Angle Glaucoma and Ocular Hypertension: A Literature Review. Annals of Pharmacotherapy. November 2020. doi:10.1177/1060028020971215

Greenstein B, Greenstein A. Medical Biochemistry at a Glance. 1st ed., Blackwell Science Ltd, Oxford, 1996: pp 117.

Gullett NP, Hebbar G, Ziegler TR. Update on clinical trials of growth factors and anabolic steroids in cachexia and wasting. Am J Clin Nutr 2010; 91(4): 1143S-1147S.

Hall M. Serotonin syndrome. Austral. Prescr. 2003; 26:62-3.

Haslett C, Chilvers ER, Hunter JAA, Boon NA. Davidson's Prin-ciples and Practice of Medicine. 18th edition, Churchill Livingstone, Edinburgh, 1999.

Hauser RA. Parkinson disease treatment & management. Emedici-ne, Medscape, 8.7.2013., dostupno na: http://emedicine.medscape.com/article/1831191-treatment#a1156, veb-stranica poslednji put posećena 4.8.2013.

Hauser SL, Cree BAC. Treatment of Multiple Sclerosis: A Review. Am J Med. 2020;133(12):1380-1390.

He ZX, Zhou ZW, Yang Y, Yang T, Pan SY, Qiu JX, Zhou SF. Overview of clinically approved oral antidiabetic agents for the treatment of type 2 diabetes mellitus. Clin Exp Pharmacol Physiol 2015; 42(2): 125-38.

Helwick C. Two Tocolytics Comparable in Postponing Preterm Labor. Medscape Multispecialty, dostupno na: http://www.medscape.com/viewarticle/839714, veb-stranica poslednji put posećena 19.8.2016.

Hentschel R, Bohlin K, van Kaam A, Fuchs H, Danhaive O. Surfactant replacement therapy: from biological basis to current clinical practice. Pediatr Res. 2020;88(2):176-183.

Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM, Schunack W, Levi R, Haas HL. International union of pharmacology. XIII classification of histamine receptors. Pharmacol Rev 1997; 49: 253-78.

Hollister LE. Clinical Pharmacology of Psychotherapeutic Drugs. 2nd ed., Churchill Livingstone, New York, 1983: pp. 214.

Holmes LB, Wyszynski DF, Baldwin EJ, Habecker E, Glassman LH, Smith CR. Increased risk for non-syndromic cleft palate among infants exposed to lamotrigine during pregnancy. Birth Defects Research 2006; 76: 5.

Hotham N, Hotham E. Drugs in breastfeeding. Aust Prescr. 2015;38(5):156-9.

Hudson SA, Boyter AC. Pharmaceutical care of the elderly. The Pharmaceutical Journal 1997; 259: 686-8.

Hull D, Johnston DI. Essential Paediatrics. 1st ed., Churchill Living-stone, Edinburgh, 1981: pp. 305.

Јанковић С. Индивидуализација дозирања антибиотика код хируршких болесника. Рад уже специјализације. Медицински факултет, Београд, 1996.

Јанковић С. Фармакологија и токсикологија, 3. издање, Медицински факултет, Крагујевац, 2011.

Јанковић С. Токсикологија, 2. издање, Медицински факултет, Крагујевац, 2019.

Janković SM, Stojković S, Petrović M, Kostić T, Zdravković M, Radovanović S, Cvjetan R, Ratković N, Rihor B, Spiroski D, Stanković A, Anđelković B, Gocić Petrović R. Results of the trycort: Cohort study of add-on antihypertensives for treatment of resistant hypertension. Medicine (Baltimore). 2023;102(22):e33941.

Jorgensen SCJ, Kebriaei R, Dresser LD. Remdesivir: Review of Pharmacology, Pre-clinical Data, and Emerging Clinical Experience for COVID-19. Pharmacotherapy. 2020;40(7):659-671.

Justiz Vaillant AA, Qurie A. Interleukin. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Kalant H, Roschlau WHE. Principles of Medical Pharmacology. 6th ed., Oxford University Press, Oxford, 1998; pp. 957.

Kang C. Sotatercept: First Approval. Drugs. 2024;84(7):857-862.

Kankaanranta H, Harju T, Kilpeläinen M, Mazur W, Lehto JT, Katajisto M, Peisa T, Meinander T, Lehtimäki L. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the finnish guidelines. Basic Clin Pharmacol Toxicol 2015; 116(4): 291-307.

Karlson P. Biokemija. 8. izd., Školska knjiga, Zagreb, 1989: 396 str.

Katzung BG. Basic and Clinical Pharmacology. 12th ed., McGrawHill Lange, Boston, 2012.

Kažić T, Rumboldt Z. Klinička kardiovaskularna farmakologija. 1. izd., Medicinska knjiga, Beograd - Zagreb, 1988: 415 str.

Keating GM. Lenograstim: a review of its use in chemotherapy-induced neutropenia, for acceleration of neutrophil recovery following haematopoietic stem cell transplantation and in peripheral blood stem cell mobilization. Drugs 2011; 71(6): 679-707.

Khan I, Kahwaji CI. Cyclobenzaprine. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-

Kirstein SL, Insel PA. Autonomic nervous system pharma-cogenomics: a progress report. Pharmacol Rev 2004; 56(1): 31-52.

Kish T, Aziz A, Sorio M. Hepatitis C in a New Era: A Review of Current Therapies. Pharmacy and Therapeutics. 2017; 42(5): 316-29.

Kobayashi T, Hara M, Shimanoe C, Morimoto T, Masaaki M, Ito K, Shimazaki T. Efficacy and safety of romosozumab: a meta-analysis of placebo-controlled trials. J Bone Miner Metab. 2024 Jul 8. doi: 10.1007/s00774-024-01531-5. Epub ahead of print.

Kostić M, Milosavljević MN, Stefanović S, Ranković G, Janković SM. Cost-utility of tafenoquine vs. primaquine for the radical cure (prevention of relapse) of Plasmodium vivax malaria. J Chemother. 2020;32(1):21-29.

Kriner P, Brieger P, Pogarell O, Schüle C, Mußmann L, Korbmacher J, Seemüller F. Treatment of bipolar depression: clinical practice vs. adherence to guidelines-data from a Bavarian drug surveillance project. Front Psychiatry. 2024;15:1425549.

Kubica J, Adamski P, Gajda R, et al. Recommendations for clinical use. Multidisciplinary experts' standpoint. Cardiol J. 2023;30(4):502-505.

Levi Setti PE, Alviggi C, Colombo GL, Pisanelli C, Ripellino C, Longobardi S, Canonico PL, De Placido G. Human recombinant follicle stimulating hormone (rFSH) compared to urinary human menopausal gonadotropin (HMG) for ovarian stimulation in assisted reproduction: a literature review and cost evaluation. J Endocrinol
Invest 2015; 38(5): 497-503.

Li, Jiayi MD; Lei, Xiangguo MD; Li, Zihao MDd; Yang, Xi MD. Effectiveness and safety of Inclisiran in hyperlipidemia treatment: An overview of systematic reviews. Medicine 2023; 102(3): e32728.

Longmore JM, Wilkinson I, Turmezei T, Cheung CK. Oxford Handbook of Clinical Medicine. 7th ed., Oxford University Press, Oxford, 2007: pp. 841.

Löscher W, Rogawski MA. How theories evolved concerning the mechanism of action of barbiturates. Epilepsia 2012; 53 Suppl 8: 12-25.

Lullman H, Mohr K, Hein L, Bieger D. Color Atlas of Pharma-cology. 3rd ed., Thieme Stuttgart, Stuttgart, 2005.

Madhusoodanan M, Borui K, Xianyou P, and Guangdi W. From Pure Antagonists to Pure Degraders of the Estrogen Receptor: Evolving Strategies for the Same Target. ACS Omega 2021 6 (14), 9334-9343.

Marabotto E, Ziola S, Savarino V, Giannini EG, Furnari M, Bodini G, Zingone F, Ghisa M, Barberio B, Zentilin P, Savarino E. Vonoprazan Fumarate for the Treatment of Gastric Ulcers: A Short Review on Emerging Data. Clin Exp Gastroenterol. 2020;13:99-104.

Маретић З. Наше отровне животиње и биљке. Стварност, За-греб, 1986.

Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020; 27(10): 1918-1929.

Mbi Feh MK, Wadhwa R. Clomiphene. 2020 Nov 7. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020

McLachlan A, Ramzan I. Meals and medicines. Austr Prescr 2006; 29: 40-2.

Merlo C, Bally K, Tschudi P, Martina B, Zeller A. Management and outcome of severely elevated blood pressure in primary care: a prospective observational study. Swiss Med Wkly 2012; 142: w13507.

Middlebrook I, Schoener B. Anabolic Steroid Toxicity. [Updated 2022 Nov 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Mu-ming Poo, New light on the horizon of Alzheimer's disease, National Science Review, 2020; 7 (5): 831.

Neal MJ. Medical Pharmacology at a Glance. 2nd ed., Blackwell Scientific Publications, Oxford, 1992: pp. 88.

Nicolas D, Kerndt CC, Patel P, et al. Sacubitril-Valsartan. [Updated 2024 Feb 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Pardridge WM. Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab. 2012;32(11):1959-1972.

Paul AK, Melson JW, Hirani S, Muthusamy S. Systemic therapy landscape of advanced prostate cancer. Adv Cancer Res. 2024;161:367-402.

Perry MC (ed): Toxicity of chemotherapy. Semin Oncol 19(5):453-609, 1992.

Pharmacopoea Jugoslavica MCMXXXIII. Kraljevina Jugoslavija, Ministarstvo socijalne politike i narodnog zdravlja, Sanitetsko ode-ljenje, Beograd, 1933: 820 str.

Plećaš D, Jovanović - Mićić D, Plećaš D, Rosić N. Osnovni lekovi u trudnoći i laktaciji. 1. izd., Nauka, Beograd, 1996: 200 str.

Poewe W, Seppi K, Marini K, Mahlknecht P. New hopes for disease modification in Parkinson's Disease. Neuropharmacology. 2020 Jul;171:108085. doi: 10.1016/j.neuropharm.2020.108085

Pokhrel B, Aiman W, Bhusal K. Thyroid Storm. [Updated 2022 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Popović J, Sabo A, Mikov M. Priručnik iz farmakologije, toksi-kologije i kliničke farmakologije (opšti deo). 1. izd., Nova Prosveta, Beograd, 1995: 144 str.

Porcaro F, Ullmann N, Allegorico A, Di Marco A, Cutrera R. Difficult and Severe Asthma in Children. Children (Basel). 2020;7(12):286.

Potter LR, Yoder AR, Flora DR, Antos LK, Dickey DM. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol 2009; (191): 341-66.

Rainer MK. Risperidone long-acting injection: a review of its long term safety and efficacy. Neuropsychiatr Dis Treat 2008; 4(5): 919-27.

Ramsey PG, Larson EB. Medical Therapeutics, 2nd ed., W.B. Saunders Company, London, 1993: pp. 633.

Rees J, Ritter J, Spector R. Aids to Clinical Pharmacology and The-rapeutics. 3rd ed., Churchill Livingstone, Edinburgh, 1993: pp. 291.

Repatha. 140 mg. Сажетак карактеристика лека, rastvor za injekciju u napunjenom injekcionom špricu. Агенција за лекове и медицинска средства Србије, 2020. Доступно на:
https://www.alims.gov.rs/ciril/files/lekovi/smpc/515-01-04683-15-001.pdf

Rice MA, Malhotra SV, Stoyanova T. Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. Front Oncol. 2019;9:801.

Rocha A, Almeida M, Santos J, Carvalho A. Metformin in patients with chronic kidney disease: strengths and weaknesses. J Nephrol 2013; 26(1): 55-60.

Rosenstock J, Bajaj HS, Janež A, et al; NN1436-4383 Investigators. Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment. N Engl J Med. 2020;383(22):2107-2116.

Röther J, Ford GA, Thijs VN. Thrombolytics in acute ischaemic stroke: historical perspective and future opportunities. Cerebrovasc Dis 2013; 35(4): 313-9.

Saleh SS, Al-Ramahi MQ, Al Kazaleh FA. Atosiban and nifedipine in the suppression of pre-term labour: a comparative study. J Obstet Gynaecol 2013; 33(1): 43-5.

Sanford JP, Gilbert DN, Moellering RC, Sande MA. The Sanford Guide to Antimicrobial Therapy. 27th ed., Antimicrobial Therapy Inc, Vienna, 1997: pp. 134.

Schaefer B, Meindl E, Wagner S, Tilg H, Zoller H. Intravenous iron supplementation therapy. Mol Aspects Med. 2020;75:100862.

Schmucker DL. Aging and Drug Disposition: An Update. Phar-macol Rev, 1985; 37: 133-148.

Schwartz SI, Shires GT, Spencer FC, Husser WC. Principles of Surgery. 6th ed., Mc Graw Hill Inc., New York, 1994: pp. 2074.

Seale JP. Anticholinergic bronchodilatators. Aust Prescr 2003; 26: 33-5.

Shipton EA. New formulations of local anaesthetics-part I. Anesthesiol Res Pract 2012; 2012: 546409. doi: 10.1155/2012/ 546409.

Shirasaka Y, Shichiri M, Murata Y, Mori T, Nakanishi T, Tamai I. Long-lasting inhibitory effect of apple and orange juices, but not grapefruit juice, on OATP2B1-mediated drug absorption. Drug Metab Dispos 2013; 41(3): 615-21.

Smith TJ, Johnson CR, Koshy R, Hess SY, Qureshi UA, Mynak ML, Fischer PR. Thiamine deficiency disorders: a clinical perspective. Ann N Y Acad Sci. 2021;1498(1):9-28.

Soff G, Leader A, Al-Samkari H, Falanga A, Maraveyas A, Sanfilippo K, Wang TF, Zwicker J. Management of chemotherapy-induced thrombocytopenia: guidance from the ISTH Subcommittee on Hemostasis and Malignancy. J Thromb Haemost. 2024;22(1):53-60.

Stanulović M (urednik). Lekovi u prometu 2008. 1. izd., Ortome-dics, Novi Sad, 2008.

Stanulović M, Sabo A, Rončević N. Klinička farmakologija dečijeg uzrasta. 1. izd., Medicinska knjiga, Beograd-Zagreb, 1991: 111 str.

Stojanović V. Ratna hirurgija, II deo. 1. izd., Naučna Knjiga, Beo-grad, 1955: 382 str.

Strasser SI. Managing hepatitis C in general practice. Australian prescriber. 2017; 40(2): 64-9.

Taylor BN, Mueller M, Sauls RS. Cannaboinoid Antiemetic Therapy. 2020 Sep 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 30571051.

The Merck Index Online. Royal Society of Chemistry, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, N.J., U.S.A., 2021. Available at: https://www.rsc.org/merck-index

Tierney LM,Jr., McPhee SJ, Papadakis MA. 2008 Current Medical Diagnosis & Treatment. 47th edition, Lange Medical Books/Mc Graw -Hill, New York, 2008.

Tiwari G, Tiwari R, Sriwastawa B, et al. Drug delivery systems: An updated review. International Journal of Pharmaceutical Investigation 2012; 2(1): 2-11.

Torkildsen Ø, Myhr KM, Bø L. Disease-modifying treatments for multiple sclerosis - a review of approved medications. Eur J Neurol 2016; 23 Suppl 1: 18-27.

Trechot P, Petitpain N, Guy C, Pinzano A, Javot L, Schmutz JL, Marie B, Barbaud A. Nicorandil: from ulcer to fistula into adjacent organs. Int Wound J 2013; 10(2): 210-3.

Varagić V, Milošević M. Farmakologija. 21. izd., Elit-Medica, Beo-rad, 2007: 724 str.

Varga Z, Sabzwari SRA, Vargova V. Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue. Cureus. 2017;9(4):e1144.

Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147-1161.

de Vries HE, Kuiper J, de Boer AG, Van Berkel TJC, Breimer DD. The blood-brain barrier in neuroinflammatory diseases. Pharmacol Rev 1997; 49: 143-56.

Wachter SB, Gilbert EM. Beta-adrenergic receptors, from their discovery and characterization through their manipulation to beneicial clinical application. Cardiology 2012; 122(2): 104-12.

Waite LM. New and emerging drug therapies for Alzheimer disease. Aust Prescr. 2024;47(3):75-79.

Wakabayashi H, Arai H, Inui A. Anamorelin in Japanese patients with cancer cachexia: an update. Curr Opin Support Palliat Care. 2023;17(3):162-167.

Waller DG, Renwick AG, Hillier K. Medical Pharmacology and Therapeutics. 2nd edition, Elsevier Saunders, Edinburgh, 2005.

Wang CM, Wu BR, Xiang P, Xiao J, Hu XC. Management of male erectile dysfunction: From the past to the future. Front Endocrinol (Lausanne). 2023;14:1148834.

Wang F, Sun L, Wang S, Davis JM 3rd, Matteson EL, Murad MH, Luo F, Vassallo R. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. Mayo Clin Proc. 2020;95(7):1404-1419.

Warrington R, Silviu-Dan F. Drug allergy. Allergy Asthma Clin Immunol 2011; 7 Suppl 1: S10.

Whalen K, Finkel R, Panavelil TA. Lippincott Illustrated Reviews: Pharmacology, Sixth Edition, Wolters Kluwer, 2015.

White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2013 Aug 14. doi:pii: S0140-6736(13)60024-0.
10.1016/S0140-6736(13)60024-0.

Widdop B. Therapeutic Drug Monitoring. 1st ed., Churchill Livin-gstone, Edinburgh, 1985: pp. 359.

Wilkins R, Cross S, Megson I, Meredith D. Oxford Handbook of Medical Sciences. 1st edition, Oxford University Press, Oxford, 2006.

Winslow BT, Onysko MK, Stob CM, Hazlewood KA. Treatment of Alzheimer disease. Am Fam Physician. 2011; 83(12): 1403-12.

Wiviott SD, White HD, Ohman EM, Fox KA, Armstrong PW, Prabhakaran D, Hafley G, Lokhnygina Y, Boden WE, Hamm C, Clemmensen P, Nicolau JC, Menozzi A, Ruzyllo W, Widimsky P, Oto A, Leiva-Pons J, Pavlides G, Winters KJ, Roe MT, Bhatt DL. Prasugrel versus clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TRILOGY ACS trial. Lancet 2013; 382(9892): 605-13.

World Health Organization. Critical Review Report: pregabalin. Expert Committee on Drug Dependence. Forty-first Meeting, Geneva, 12-16 November 2018. Dostupno na: https://www.who.int/medicines/access/controlled-substances/Pregabalin_FINAL.pdf

Ws A. Use of Antiplatelet Drugs in the Treatment of Acute Coro-nary Syndromes. Cardiovasc Hematol Disord Drug Targets. 2013 Jul 5. [Epub ahead of print] PubMed PMID: 238631