MANUAL OF PHARMACOLOGY AND TOXICOLOGY

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- sixth, amended and revised edition -

GENERAL PHARMACOLOGY

PHARMACODYNAMICS

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

A drug is any substance introduced into the body that improves or cures a disease, prevents it or helps in the diagnosis of a disease. A poison is a substance that, taken into an organism in a relatively small dose, causes its damage or death. The boundary between poison and medicine is sometimes very unclear: the same substance can be both medicine and poison, depending on the dose used. For example, cardiotonic glycosides in therapeutic doses are very effective drugs that can help a lot in heart failure; but if their dose is increased just a few times, they can lead to heart rhythm disturbances and even death. Even ordinary **water can be poison: cases of** *psychogenic polydipsia* have been described due to the fact that people drank 6-7 liters of water in a few hours. It resulted as edema of the lungs and brain with a fatal outcome. Paracelsus, a physician from the 16th century, noticed the vague border between medicine and poison, saying: "All substances are poisons, there is not one that is not. Only the dose depends on whether something will be a medicine or a poison**.** "

The largest number of drugs act by binding to a specific place in the body, which we call ***a receptor***. A receptor is always a macromolecule, usually 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 the endogenous ligand most often start a series of reactions in the cells on which the receptor is located. The result is a specific effect of the endogenous substance. The receptor is actually switched to an activated state upon ligand binding. Drugs that bind to receptors are chemically similar to endogenous ligands. If the drug causes changes in the shape of the receptor similar to the changes that occur after the binding of the endogenous ligand (ie, the receptor goes into an active state), we call such a drug **an agonist** . On the other hand, if the drug does not cause any shape changes after binding to the receptor (ie, the receptor remains in an inactive state), but only interferes with the binding (and thus the action) of the endogenous ligand, we call such a drug 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 the herb, binds to muscarinic receptors and keeps them in an inactive state, so it is called a muscarinic receptor *antagonist.*

Agonists and antagonists can bind to the **same** site on the receptor to which the endogenous ligand binds. If that is the case, we speak of ***orthosteric*** binding and possible interaction between the endogenous ligand, agonist or antagonist. If the drug binds to a **different site** on the receptor compared to the one to which the endogenous ligand binds, and if binding leads to a

strengthening or weakening of the effect of the endogenous ligand, we speak of ***allosteric*** binding and 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 an endogenous ligand is not bound to them.

Some receptors are activated even without an endogenous ligand, i.e. they are constitutionally active. Endogenous ligand inactivates such receptors, i.e. causes a conformational change in them that interrupts their activity. Medicines that bind to such receptors, and which, like endogenous ligands, cause a conformational change that translates the receptor into an inactive state, are called **inverse agonists**. An example of constitutively active receptors are receptors for melano-stimulating hormone, type MC $_4$, which reduce the feeling of hunger. Their endogenous ligand, the so-called agouti-related peptide, acts as *an inverse agonist* , i.e. the receptor translates into an inactive state, which increases the feeling of hunger.

There is a small number of drugs that do not act through the receptor mechanism, but in other ways. For example, the osmotic diuretic mannitol promotes the excretion of water from the body because it creates a high osmolarity of the primary urine and thus prevents water reabsorption. Such are antacids: drugs that, as weak bases, directly neutralize hydrochloric acid in the stomach after oral intake. However, receptor binding remains by far the most common mechanism of drug action.

CONNECTIONS OF DRUG WITH RECEPTOR

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

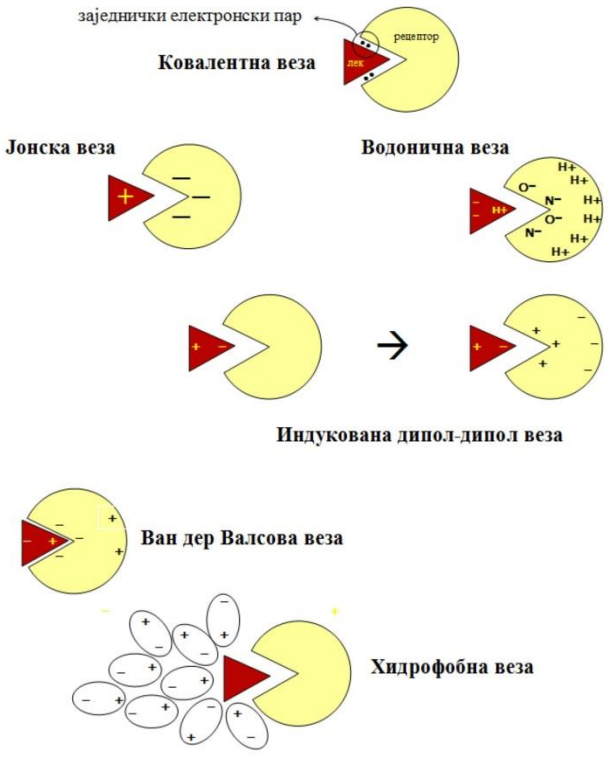


Figure 1. Connections of the drug with the receptor.

Finally, the drug and the receptor which are very hydrophobic, can come into contact because the dipoles of water push them out of themselves. We call that effect ***a hydrophobic bond***.

Several types of bonds often play a role in the binding of a drug to a receptor. 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 binding site on the receptor, the drug gets close enough to establish van der Waals bonds, and for the receptor to be activated or inactivated.

OPTICAL ISOMERY

If the drug has a carbon atom in its molecule that is attached to 4 different groups, then it can exist in two isomeric forms that differ from each other in terms of chemical composition only by the spatial arrangement of the groups attached to that so-called. asymmetric carbon atom (Figure 2). However, these two forms are very different from each other in terms of 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 possessing optical isomerism can only be obtained as an equimolar mixture of both isomers. We call such mixtures racemates. Their application is sometimes fraught with difficulties because isomers can have completely opposite effects.

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

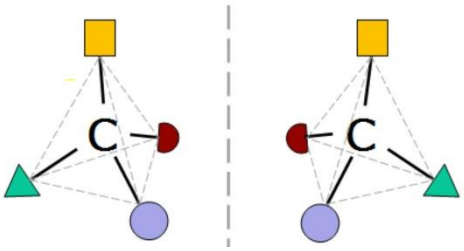


Figure 2. Optical isomerism

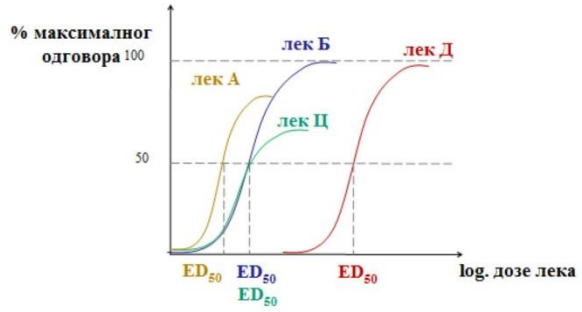
DRUG AND RECEPTOR INTERACTION

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

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

It is usual to present the drug concentration on a logarithmic scale in the graphic representation of the gradual (graded) response. This theoretical dependence of the organism's response or a part of it on the concentration of the free drug in the receptor's vicinity has been confirmed many times experimentally. 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 on the same experimental system (eg, on an isolated organ), we can compare the affinity of those drugs for the receptor they act on as well as 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 more dose-response curve is shifted to the left, the greater is the affinity (i.e. if the effect can be achieved with smaller doses of the drug). On the other hand, the mere binding of the drug to the receptor does not mean that it will cause changes in the receptor, and thus in the cell, i.e. does not mean that the medicine will also have ***internal activity***. We measure it by the size of the maximum effect that can be achieved with a given drug. In the following picture, drug A has a higher affinity for receptors than drug B, but therefore the internal activity of drug B is significantly higher. If we measure the effects of the drug on the whole organism (in vivo), then instead of affinity we talk about the strength of the drug's effect, and instead of internal activity, we talk about the effectiveness of the drug. These quantities are not uniquely related: if we apply drugs to the whole organism, the absorption, metabolism and excretion of the drug also affect the final effect of the drug. In practice, the most important thing is ***the effectiveness*** of the drug, because the success in the treatment of the patient depends on it. Very rarely, the potency of a drug is so low that it makes practical application of the drug difficult.



Лек А је најјачи (има најмању ED_{50}), лекови Б и Ц су подједнако јаки, а лек Д је најслабији.

Лек Ц је најмање ефикасан, потом лек А, док су лекови Б и Д подједнако ефикасни.

При избору лека, за терапеута ефикасност лека има већи значај од јачине.

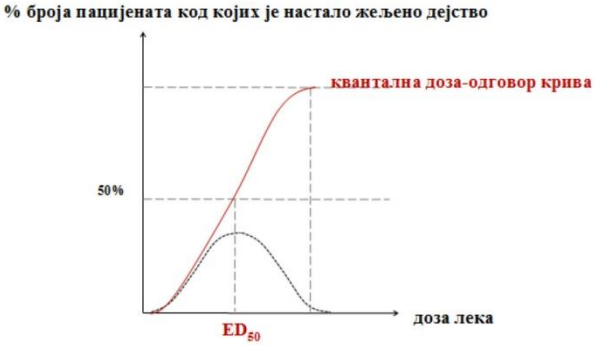
Figure 3. Concentration-response curves for drugs that act on the same receptor and differ in affinity and intrinsic activity.

The effect of drugs that act on the principle of "all or nothing" can also be graphically displayed, using the so-called dose-response quantal curves. 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 ypsilon-axis, we will get a sigmoid curve. From such a curve, we can determine **the drug dose at which 50% of patients will respond to the drug**. Such a dose is called "effective dose 50%" (ED_{50}).

Sometimes the body's response to a drug is "either...or..." ("all or nothing"), e.g. the drug either interrupts the convulsive attack or it does not. Then we cannot talk about 50% of the desired effect, but about the number (percentage) of **patients** in whom the desired effect occurred.

Figure 4. Gaussian normal variation curve

By summing the responses for each dose, a quantal dose-response curve is formed. ED50 in that case is the drug dose that causes the desired effect in 50% **of patients :**



D50 and LD50) are determined .

Figure 5. Quantal relationship between dose and drug effect

INTERACTIONS BETWEEN MEDICINES

Two drugs that we administer at the same time can affect each other so that their overall effect decreases or increases. That influence of one drug on another can take place during their absorption, distribution, metabolism or excretion. That is called **pharmacokinetic interactions.** On the other hand, if we talk about the drug influence at the very place of their action on the target tissue or organ, we talk about **pharmacodynamic** interactions. If two drugs work together so that their overall effect does not decrease or increases, then we call such drugs synergists. **Synergism** can be ***additive*** (when the total effect of both drugs is equal to the simple sum of the effects of both drugs for each other) or ***potentiating*** (when the total effect of both drugs is greater than the simple sum of the effects of both drugs separately). Non-steroidal anti-inflammatory drugs act additively, while potentiating synergism is shown by e.g. a combination of two chemotherapy drugs, 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 it is **antagonism** (note: this is antagonism *between two drugs* and not an antagonistic effect of the drug on the receptor, which was discussed in the previous chapter). Antagonism can be of ***a chemical nature:*** when two drugs are chemically bound to each other and thus inactivated. An example of this is penicillin and gentamicin, which must never be used in the same syringe. Medicines can antagonize the effect of each other in all phases of their movement in the body: during absorption, distribution, metabolism and excretion, reducing the available amount of medicine near the receptor. An example of the interaction of two drugs during *absorption* is the simultaneous oral administration of doxycycline (a tetracycline antibiotic) and iron sulfate; iron binds to doxycycline, and a complex is formed that cannot be absorbed from the intestinal lumen into the bloodstream. A potential place where drugs can affect each other during *distribution* are plasma proteins, primarily albumins. Since the number of drugs bind to albumin in a high percentage, it can interfere with binding to each other in the case the drugs are administered at the same time. This can also increase the concentration of the free fraction of the drug in the plasma.

However, the increase in the free fraction of a drug in the plasma is accompanied by the acceleration of its metabolism. Due to the fact that it enters the hepatocytes to a greater extent, the end result of the interaction on albumins will not be an increase in the effect of the drug, i.e. these interactions have no clinical significance. An example of drug interaction in the course of *metabolism* is an increase in the concentration of the antiepileptic drug carbamazepine in the blood when it is administered simultaneously with clarithromycin or erythromycin or antibiotics that inhibit cytochrome CIP 3A4 and thus interfere with the metabolism of carbamazepine. During *the excretion* of drugs, a well-known example of an interaction with clinical significance is the increase in the concentration of the cardiotonic digoxin in the blood, which occurs due to the blockade of the drug's tubular secretion by the antiarrhythmic amiodarone.

Medicines can act on the same organ in the opposite direction. 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 place on the receptor, so that the one of them has internal activity and the other 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 internal activity, is called an agonist, and the second, which does not, is called an antagonist.

If the antagonist binds to the receptor with non-covalent bonds, then by increasing the concentration of the agonist, we can displace the antagonist from the receptor and again achieve the same effect with the agonist. We call such antagonism ***competitive*** or ***reversible antagonism***. This type of antagonism includes, for example, homatropine, which blocks muscarinic receptors, and pilocarpine which activates them.

On the other hand, if the antagonist binds 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 administration of the antagonist. The reason for this is the fact that those receptors to which the antagonist binds have been irreversibly changed and thrown out of function. 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 internal activity after binding to the receptor (meaning they cause some effect), but it is significantly less than the internal activity of other drugs that bind to the same receptor. Such drugs are called ***partial agonists***. If we apply them together with drugs that have full internal activity (***full agonists***), then partial agonists will reduce the effect of full agonists because they will occupy a number of receptors and cause a smaller effect than full agonists. That's why we often call partial agonists partial antagonists. An example of a partial agonist is nalor-fin. If administered alone, it has a weak analgesic effect, but if administered together with morphine (a full agonist), it reduces the effect of morphine and acts as a partial antagonist.

THERAPEUTIC WIDTH AND THERAPEUTIC INDEX

The selectivity of the drug is the property of the drug to act only in one place in the body without affecting the function of other tissues and organs. Unfortunately, not a single drug is absolutely selective, but more or less acts on other places in the body. Often these other effects are unfavorable for the organism, so we call them ***unwanted effects***. If they imply significant damage to the tissues of the organism and if they occur when the drug is used in doses *higher than recommended*, we call them ***toxic effects***. The range between the minimum dose of the drug that causes a beneficial effect in the body and the minimum dose of the drug that causes a toxic effect is called ***the therapeutic range of the drug***. The medicine is all the more suitable for application if its therapeutic width is greater.

Another measure of the selectivity of the drug effect is ***the therapeutic index***. It is the ratio of the drug dose that causes a toxic effect in 50% of patients *(TD_{50})* and the drug dose that causes the desired effect in 50% of patients *(ED_{50})*. 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 concentrations of the drug that lead to the desired, i.e. toxic effects in 50% of patients, as seen in the picture.

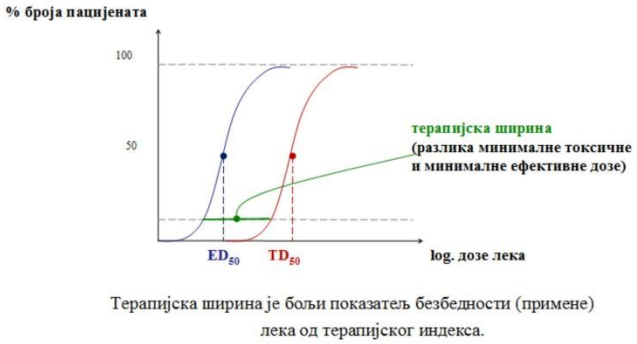


Figure 6. Therapeutic index and therapeutic width

If the drug has a higher therapeutic index (similar to the therapeutic range), its application is simpler and safer. Since one drug can have several side effects, it will also have several therapeutic indices: as many side effects as it has. Sometimes the therapeutic index for some of the milder side effects is called *the protective index* (for example, the ratio of ED_{50} of phenobarbitone for sedative effect and ED_{50} of phenobarbitone for anticonvulsant effect (prevention of convulsions).

RECEPTOR FAMILIES

Receptors for most drugs and endogenous substances can be classified into several groups based on the similar mechanism by which they function. Since each of these groups is thought to have arisen during evolution from a common ancestor - one could tentatively say "primitive receptor" - we call them receptor families. For now, we know of four large families, the so-called superfamilies: ***receptors ion channels, receptors membrane enzymes, receptors linked to G-proteins and intracellular receptors*** .

Receptors representing ion channels are located in the cell membrane and are closed at rest. When an agonist (drug or some endogenous substance) binds to such a receptor, conformational changes occur in it and an opening (channel) is created through which ions can pass. Since there are different concentrations of ions on both sides of the membrane, they now pass through the channel from a place of higher concentration 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 receptor ion channels are nicotinic receptors (channels for sodium ions) 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 these receptors until the appearance of the effect is measured in milliseconds.

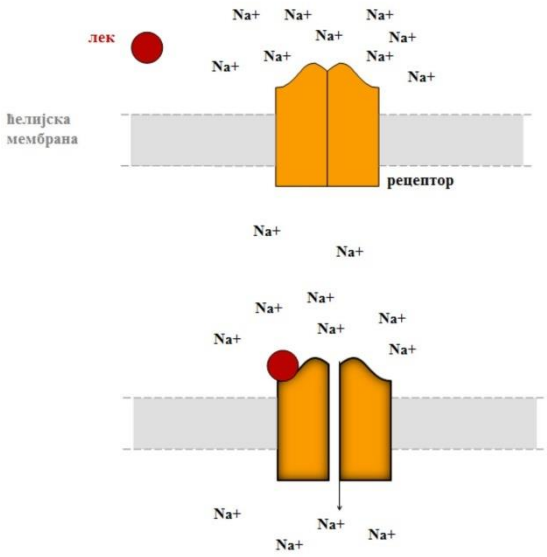


Figure 7. Receptor ion channels

Another superfamily of receptors is also found in cell membranes functioning as **a membrane enzyme.** The receptor bridges the lipid layer 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 that functions as an enzyme. At rest, the enzymatic part of the receptor is inactive; however, after binding the drug to the outer part of the receptor, it activates and catalyzes a certain biochemical reaction. The receptor for the hormone insulin belongs to this group. Its enzymatic part acts as a tyrosine kinase, i.e. phosphorylates the amino acid tyrosine in intracellular enzymes, leading to their activation. The time that passes from the binding of the drug to the receptor until the appearance of the effect is measured in minutes.

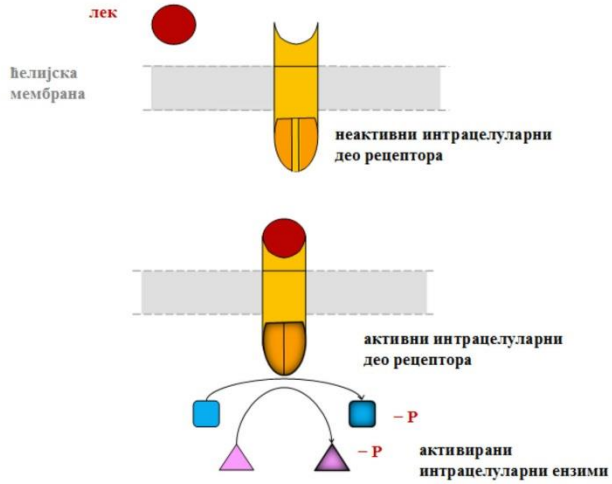


Figure 8. Receptor transmembrane enzymes

One subtype of transmembrane enzyme receptors are cytokine receptors (growth hormone, erythropoietin, interferons and others). In them, the part of the receptor on the inner side of the membrane is not an enzyme, but is in close contact with the enzyme; most often, that enzyme is 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, where it regulates the transcription of certain genes.

Receptors bound For G - proteins are very much numerous. They include: adrenergic αand βreceptors, muscarinic receptors, dopamine receptors and many others. They structurally characterize by the fact that their own peptide chain passes for seven times from the end to the end of the cellular membranes.

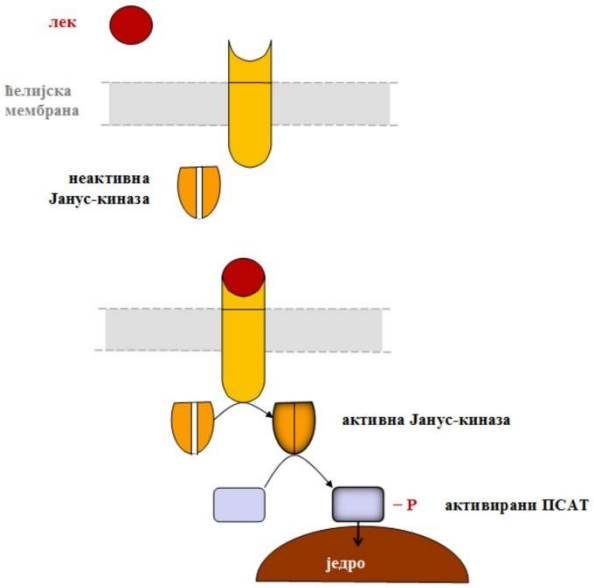


Figure 9. Cytokine receptors.

Medicines or endogenous substances (we also call them endogenous ligands) bind for a part of receptors with external sides membranes and cause conformational changes that activate intracellular part of it. This activation done, the intracellular part of receptors enters in interaction with G - protein. G - proteins are on the internal sides membranes and consist of the three subunits: α, β and γ. We call them G - proteins because they bind guanosine - triphosphate (GTP) for αsubunit, while they disassociate the subunits as β and γ are after interactions with the intracellular part of receptors. Activated as described, αsubunit can have different functions inside of cells depending on the different kinds of G - protein. αsubunit inhibits the enzyme called adenylate cyclase when some of G – proteins are in question; on the contrary, it can stimulate this enzyme concerning the rest of them. This enzyme creates cyclical adenosine monophosphate (cAMP) as an important intracellular secondary messenger. This kind of subunit activates enzyme phospholipase C when the third group of G-proteins is in question: this enzyme creates two secondary intracellular messengers called diacyl - glycerol and inositol – triphosphate. These messengers are created from the membrane phospholipids that is called phosphatidyl – inositol. All of secondary messengers further activate or inhibit different intracellular functional proteins, which can result with the reaction of the cell (if the muscular cell is in question, it can contract or relax and if the cell of exocrine or endocrine glands is in question, it can secrete its own product). αsubunit needs energy to manifest its effect. The subunit gets this kind of energy by decomposition of GTP into the guanosine diphosphate (GDP) and the phosphorous acid. After manifested effect, αsubunit inactivates under the influence of GDP and binds again for β and γsubunit. That's how the whole G - protein passes in the state of rest which lasts until medicine binds for receptor all over again.

The time that elapses from the binding of the drug to the receptor until the appearance of the effect is measured in seconds.

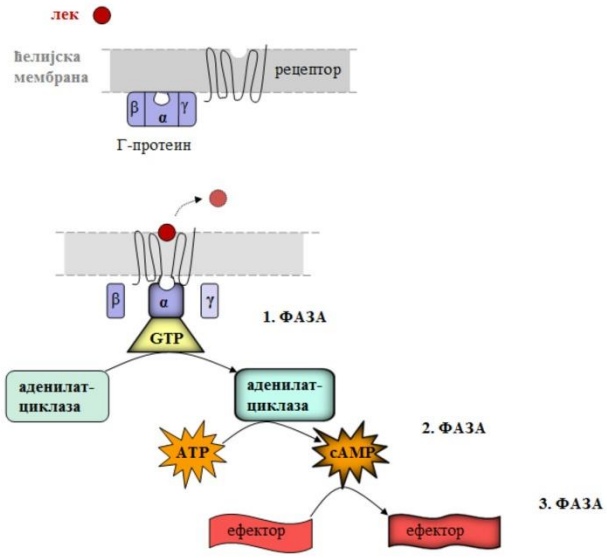


Figure 10. Receptors linked to G-proteins.

Only substances that are liposoluble can bind to **intracellular receptors (some of them are in the cytoplasm and some are in the nucleus)** which 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. The binding of these substances to the receptor leads to the creation of a drug-receptor complex that regulates gene expression: it increases the transcription of some genes and decreases the transcription of other genes. The end result is increased synthesis of enzymes and other functional proteins of the cell. Since protein synthesis takes time, these drugs manifest their effect clinically only after a latent period (the first effects are seen after one hour, and the full effect is seen only after 24 hours).

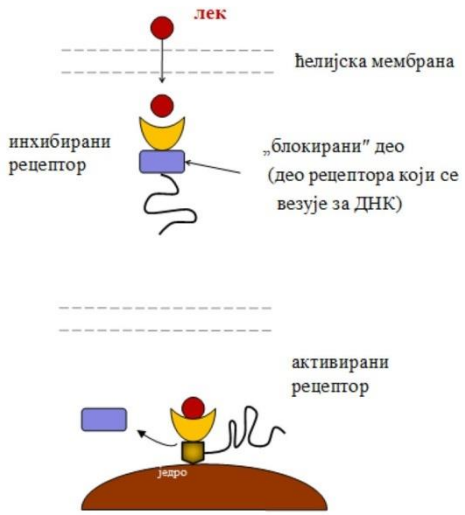


Figure 11. Intracellular receptors

SECONDARY GAZETTEERS

As already mentioned in the previous chapter, the activation of the receptor by the drug leads to the creation of signaling molecules inside the cell, which trigger a series of changes in the cell and ultimately lead to an effect (eg contraction, secretion, etc.). We call such signaling molecules secondary messengers. The most important secondary messengers are cyclic adenosine monophosphate (cAMP), calcium and phosphoinositides as well as cyclic guanosine monophosphate (cGMP). Secondary classifiers enable amplification of the signal created by the binding of the agonist to the receptor.

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

Some of the G-protein-coupled receptors and transmembrane enzyme receptors can activate the membrane enzyme phospholipase C after agonist activation. This enzyme breaks down one phospholipid from the cell membrane, phosphatidylinositol-4,5-bisphosphate, into two secondary messengers: diacylglycerol and inositol-1,4,5-triphosphate. Diacylglycerol remains in the membrane and there it activates another membrane enzyme, protein kinase C. Inositol-1,4,5-triphosphate goes 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 ceases with dephosphorylation, so that diacylglycerol is either incorporated back into phospholipids or is 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 smooth muscle cells of blood vessels, cGMP regulates the activity of enzymes from the kinase group, which ultimately leads to ***dephosphorylation of myosin light chains*** and cell relaxation. cGMP is produced by either cytoplasmic guanylyl cyclase or membrane guanylyl cyclase. Cytoplasmic enzyme activates nitric oxide (NO), previously created in endothelial cells, under the action of acetylcholine, histamine or some other mediators. Membrane guanylyl cyclase is actually the internal part of the transmembrane enzyme receptor, which binds the hormone atrial natriuretic peptide (A NP) from the outside of the membrane.

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

BIOLOGICAL STANDARDIZATION

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

Over time, due to the progress of pharmaceutical technology, some preparations that were previously measured using international units were synthesized or isolated in pure form. Then it is simple to measure the dose in weight units (for example, 1 international unit of vitamin D_3 contains 0.025 μg of the pure substance).

PHARMACOKINETICS

Absorption and distribution medicines

Absorption

The movement of drugs in the body begins with the absorption process. Drug absorption is the process of drug movement from the site of administration to the bloodstream. On that way, the only real obstacle are lipid membranes through which the drug can pass in one of the two most significant ways: diffusion, provided as sufficiently lipophilic, and 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 only be absorbed if they become sufficiently lipophilic. As most drugs are chemically either a weak acid or a weak base, they will be all the more lipophilic if they are less ionized, i.e. less dissociated. The degree of their ionization is mostly influenced 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 non-ionized, and therefore 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 lipid membranes very poorly. The opposite happens if the environment is more basic (high pH): then weak acid drugs will be ionized and weak base drugs will be non-ionized.

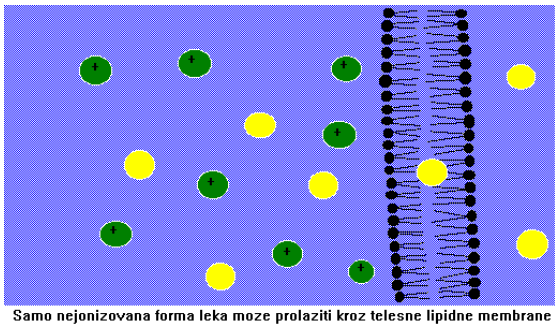


Figure 12. Passage of drugs through lipid membranes

Therefore, the pH of the environment is one of the most important factors that affects the absorption of drugs by changing their ionization, that is, 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 found 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 OATP1V, which are found on both enterocytes and hepatocytes. These transporters are also important in terms of drug 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. antihistamine fexofenadine.

Apart from diffusion or specific transport, smaller amounts of the drug can pass through the lipid membrane **by endocytosis**. In this way, mostly drugs whose molecules are proteinaceous pass through. Only drugs with a molecular weight below 100 daltons can use another way of passing through lipid membranes: **filtration**, i.e. free passage through the pores for water in the membranes. There are few such drugs (e.g. ethanol, urea), so this way of passing through membranes is not very important.

If the drug is administered **intravenously, we call it *injections***. By injecting someone, we introduce the medicine directly into the blood through a needle inserted into a vein. This way of administering drugs allows quick and complete drug delivery into the blood and quick onset of action, which is very important in emergency situations. However, this method of administration is also very risky: the drug must be given slowly enough (intravenous injection should always be given for longer than two to three minutes), otherwise the concentration of the drug in the blood can instantly rise to a toxic level. With drugs that have an effect on 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 cause of AIDS. One should always bear in mind the fact that emulsions and drug suspensions must not be administered intravenously due to the occurrence of lipid embolism; moreover, any injection of air or gas intravenously leads to air embolism. One of the ways to reduce the risks of intravenous injection of drugs is the administration of drugs in the form of ***intravenous infusion***: the drug is dissolved in more than 100 ml of a simple physiological solution and administered drop by drop through a needle inserted into the patient's vein. This ensures a gradual delivery of the drug into the blood and avoids the possibility of high, toxic drug concentrations. Intravenous infusion can be ***continuous*** (when it lasts without interruption) or ***intermittent*** (when after the expiration of the appropriate dose it is interrupted until the next dose is administered). The speed of intravenous infusion depends on (1) **the diameter of the intravenous set** which determines how many drops there are in one milliliter of solution. It also depends on (2) **the number of drops per minute** to which we set the drip chamber using a clamp with a wheel.

We call all routes of administration of drugs, except oral and rectal route, by one name that is: parenteral administration of drugs. Intravenous administration of drugs is one of the types of parenteral administration. Other ways of parenteral drug administration are subcutaneous injection, intramuscular injection, intrathecal and epidural injection, transdermal administration and administration through the respiratory tract.

Subcutaneous and intramuscular injection of drugs represent the application of the drug through a needle into the subcutaneous or muscle tissue. From the site of application, the drug must be absorbed in order to reach the blood. As the capillaries in the subcutaneous and muscle tissue have large pores (they allow protein molecules of 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 on the speed of blood flow in the tissue. Due to the better blood supply of muscle tissue, drugs are absorbed much faster after intramuscular than after subcutaneous administration. Strongly ionized drugs that are otherwise not absorbed at all from the digestive tract can also be administered through these routes. Medicines that strongly irritate the tissue are not administered in the form of subcutaneous injection, because they can lead to necrosis of the skin, most likely due to thrombosis of the blood vessels that feed the dermis from the subcutaneous tissue.

Often, medicines for subcutaneous or intramuscular injection are deliberately prepared in the way that the absorption of the medicine is very slow, and that in order to maintain sufficient concentrations of the medicine in the blood for a long time (sometimes for weeks). This is usually done either by forming esters of the drug with long-chain fatty acids that break down slowly or by placing the drug in a medium that is difficult to absorb. We call such preparations depot injections. The antipsychotic risperidone is also produced as a depot preparation; there, 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. Using an injection every 2 weeks ensures stable concentrations of risperidone in the blood, and thus a therapeutic effect.

Intrathecal drug administration involves injecting the drug into the subarachnoid space, i.e. into the cerebrospinal fluid. ***Epidural administration of the drug*** represents the injection of the drug into the epidural space, i.e. outside of the dura mater. Both types of injection are administered in the lumbar region, between the L_3 and L_4 vertebrae. Intrathecal administration was once widely used for the treatment of bacterial meningitis and encephalitis with antibiotics that poorly penetrate the central nervous system (penicillins, aminoglycosides). However, it turned out that such application of antibiotics was associated with a high frequency of arachnoiditis and epileptic seizures, so such practice was abandoned. Today, these forms of drug administration (epidural injection) are used a lot for the treatment of severe pain in malignant diseases, because morphine can be administered in very small doses, and its effect lasts much longer than after the conventional method of administration.

Transdermally, we can only apply drugs that are highly liposoluble, 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. Absorption of the drug is slow, so high concentrations of the drug are maintained in the blood for a long time. It is even more important that this kind of application avoids the drug immediately passing through the liver, which prolongs the life in the blood of those drugs that are metabolized very quickly in it. Today, nitroglycerol, an organic nitrate with a beneficial effect on angina pectoris, and fentanyl, an opioid analgesic for the treatment of pain in cancer patients, are most often used in this way.

Medicines can also be administered ***through the respiratory tract.*** This is how beta-adrenergic agonists are most often used because of their local effect in the treatment of asthma attacks (they relax the bronchial musculature). We also apply anesthetic gases and vapors through the respiratory tract, because they affect the central nervous system. This method of administration is very fast and effective (the surface of the alveolar membrane of the lungs is as much as 70 m^2 and its thickness is only 0.2 micrometers), but difficult to control. That's why it is associated with the danger of an overdose.

So far, ***oral administration*** remains the most common method of drug administration. It is the simplest and easiest for the patient - he just needs to swallow the medicine. Oral administration is also the safest because the absorption of the drug is much slower compared to other ways of administration, so the drug rarely reaches highly toxic concentrations in blood. Drugs are practically not absorbed in the stomach, except for: (1) small amounts of drugs that are weak acids (eg acetylsalicylic acid, paracetamol, ascorbic acid, etc.) and (2) alcohol. However, the stomach can act as **a "waste"** of drugs with weak bases, even if they are administered parenterally. Medicines with a weak base are mostly undissociated in the blood, so they easily diffuse from the blood and through the stomach wall into its lumen. Due to the high acidity of the gastric juice, drug molecules that have reached the lumen of the stomach dissociate, and thus become polar, i.e. they can no longer pass through the stomach wall back into the blood (this is also popularly called "ion trapping"). Thus, a part of the drug with a weak base is withdrawn from the systemic circulation into the lumen of the stomach, thus weakening the overall effect of the drug on the target tissue.

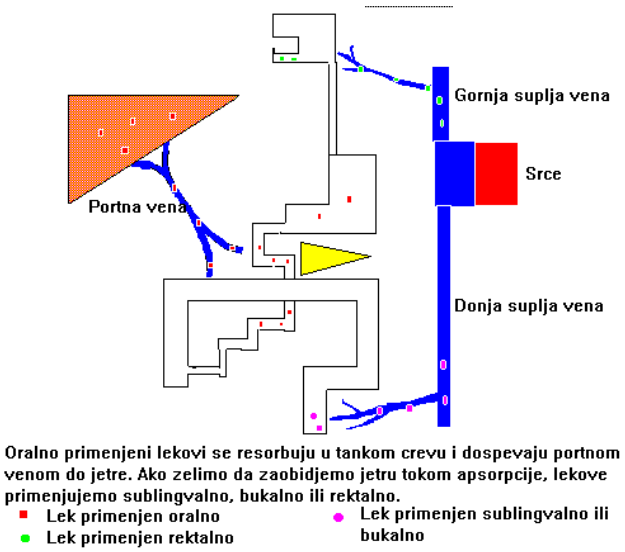


Figure 13. Absorption from the gastrointestinal tract

Most of the absorption of medicines takes place in the small intestine, which is characterized by a very large absorption surface and excellent blood supply (medicines 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 lipophilic enough) or by active transport (if they have a specific transporter). The absorption of drugs from the digestive tract is influenced by many factors. Firstly, the speed of gastric emptying determines the speed with which the drug will reach the absorption site, i.e. into the small intestine. The medicine taken before a meal reaches the small intestine quickly, after 10 to 15 minutes. But, if taken after a meal, the entire amount of medicine will reach the small intestine only when the stomach is completely empty, which means after 3 to 5 hours. Secondly, the rate of peristalsis of the small intestine can have a significant effect on absorption. If the rate is too high (as with all forms of diarrhea) the drug will reach the large intestine before significant absorption takes place. Thirdly, the food that the patient takes during the administration of the drug can significantly affect the absorption. For example, if the patient takes dairy products during the administration of tetracycline, a good 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 a hard time tolerating the medicine they take orally, and they feel nauseous, which can lead them to stop taking the medicine. This happens especially often with drugs that irritate the stomach lining, e.g. iron preparations, tetracyclines, serotonin uptake blockers. In such a situation, patients should be advised to try to take the medicine during a meal, or, if the medicine is given only in one daily dose, to take the medicine immediately before going to bed.

The absorption of drugs in the small intestine is influenced by two separate processes. Since drugs actually pass ***through*** epithelial cells during absorption, they are also affected by the detoxification mechanisms that these cells have.

The first mechanism of detoxification is the metabolism of drugs in the endoplasmic reticulum of epithelial cells, on cytochrome R 450. So far, isoforms **3A4, 3A5,** 2 S 9 **and** 2 S 19 of this cytochrome have been discovered in the epithelial cells of the small intestine, which can inactivate a large part of the absorbed drug, and thus prevent its entry into the blood. For example, due to these enzymes in the epithelial cells, only 20% of the orally administered immunosuppressant ciclosporin reaches the blood unchanged. *Another mechanism* that hinders the absorption of drugs in the small intestine is the pumps (transporters) on the luminal membrane of the epithelial cells, which push the drug that has entered the cell back into the lumen. The most important of these pumps is **glycoprotein R.** It is interesting that there are a large number of drugs, which are simultaneously substrates for cytochrome 3A4 and glycoprotein R, so their absorption in the small intestine is difficult for two reasons.

All drugs that are absorbed in the digestive tract reach the liver first through the portal blood stream. If the drug is extensively metabolized in the liver, only a small percentage of the ingested amount will reach the systemic circulation. We say that such drugs are *metabolized during the first passage through the liver*. The best-known example of such drugs are organic nitrates whose metabolism is so fast that the oral route of administration is possible only if the dose of the drug is increased tenfold.

Only if the drug is administered intravenously, the entire dose reaches the systemic circulation. With all other methods of administration, only part of the dose of the drug reaches the systemic circulation (this is especially pronounced with oral administration, where a good part of the dose is not absorbed or is broken down during the first passage through the liver). **The bioavailability** of a drug represents 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 from a 40 mg oral dose of this drug, only 25%, i.e. 10 mg reach the systemic circulation from where it can pass into the central nervous system and exert its effect. We determine the bioavailability of the drug by administering the drug both orally and intravenously; then we measure drug concentrations in the serum every hour after drug administration and form serum drug concentration/time curves for both methods of administration (in a coordinate system where the x-axis shows the time elapsed since drug administration, and the epsilon-axis shows the drug concentration in serum). When we calculate the area under the curve of serum drug concentration/time after oral administration and the area under the curve of serum drug concentration/time after intravenous administration, and divide one by the other (PIK oral/PIK intravenous), we get the so-called ***absolute bioavailability*** of the drug. *Relative* bioavailability is calculated when we compare two different medicinal preparations with the same active substance, after the same route of administration - oral.

To avoid the effect of the first passage through the liver, many drugs are administered sublingually, buccally or rectally (Figure 7). We administer drugs ***sublingually*** by placing a specially prepared tablet, called a lingual tablet, under the patient's tongue and waiting for it to dissolve in the mouth. ***Buccal application*** is performed according to the same principle, only the buccalette is placed in the sulcus between the gums and the mucous membrane of the cheek. In both cases, the resorption of the drug is very fast and bypasses the liver, because the drugs reach the systemic circulation directly through the superior vena cava system. However, a condition for such application 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. The medicine applied in the form of a suppository will be absorbed in the lower two-thirds of the rectum. As the inferior and middle hemorrhoidal veins draining blood from the lower two-thirds of the rectum flow directly into the inferior vena cava system, the drug will not need to pass immediately through the hepatic circulation. Also, we rectally apply drugs that have an irritating effect on 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 temperature followed by vomiting.

New systems for drug administration

Much has been done recently to develop the 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 administration of the drug. The capsule contains numerous beads of inert material (usually polystyrene, i.e. the material from which Styrofoam is made) which are coated with a layer of medicine. When the beads are released from the capsule, the medicine is slowly released from them, so the absorption is extended and the medicine remains longer in the patient's blood, with lower concentrations than with ordinary oral preparations. This ensures that the drug works longer and that side effects (which occur at higher concentrations) are less pronounced. ***Immunoliposomes*** are currently the most perfect method for targeted delivery of highly toxic cytostatics to tumor cells. Ordinary liposomes are tiny balls made of two or more layers of phospholipids, in which there is a drug, e.g. cytostatic doxorubicin. Immunoliposomes contain a variable part of a monoclonal antibody against an antigen on a tumor or other cell in the phospholipid layer. When immunoliposomes are injected into a patient intravenously, 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, the drug (eg cytostatic) is released in the tissue of the tumor itself and penetrates into the tumor cells. The administration of drugs contained in ***nanoparticles*** (balls) made of branched polyesters that are non-toxic and quickly degradable, or in liposomes, through inhalation allows the drug to remain in the lung tissue for a longer time, and thus to dose less often. In such a way (by inhalation of nanoparticles) the prostaglandin analogue iloprost is used 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 (eg sulfasalazine administration in ulcerative colitis) or when the drugs themselves are sensitive to the action of gastric acid or pancreatic enzymes (eg peptides). This is achieved by making capsules from polysaccharides (primarily *galactomannan*) that do not break down in the stomach and small intestine, but only when they reach the large intestine and that under the influence of bacteria.

Distribution

After reaching the blood, the drugs move further in the body to all tissues. We call this process drug distribution. How far will the drug reach the body, i.e. which tissues it will penetrate depends mostly on its physico-chemical characteristics, i.e. from its molecular structure. If we know the structural formula of the medicine, 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 polarization of the molecule at physiological pH values in body fluids. We can look at any 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 medium.

Water-soluble drugs are mostly ionized at rN = 7.36 - 7.40, which represents the normal concentration of hydrogen ions in blood and extracellular fluid. If such drugs have larger molecules than 100 daltons (which is the case with most drugs), they can pass through the body's membranes (which actually represent a continuous lipid layer) in only two ways: by the gradual diffusion of non-ionized molecules (which are then liposolubins) 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 hematoencephalic barrier, which can also be considered a continuous lipid layer (endothelial cells in the capillaries of the brain are firmly connected to each other so that there is no free passage between them). Only liposoluble drugs penetrate to a significant extent into the central nervous system (CNS). with a molecular weight of less than 400 daltons and those hydrosoluble drugs , i.e. liposoluble with large molecules, for which there are specific transport systems. It is clear that these will be those drugs whose chemical composition resembles endogenous water-soluble substances (eg amino acids) for which transport systems were created during evolution because they are necessary for the normal functioning of the CNS. One such drug is α-methyldopa, a centrally acting antihypertensive. It is interesting that in the testicles there is a hemato-testicular membrane that has similar characteristics to the hematoencephalic membrane.

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

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

A lot of work is done on the formulation of water-soluble drugs where they are ***attached to nanoparticles*** in order to increase their penetration through the hemato-encephalic barrier. Nanoparticles are made of degradable polymers, and drug molecules are attached to them in various ways. When the nanoparticle reaches the brain capillaries, it binds to receptors on the surface of the endothelial cells, which then carry out endocytosis of the nanoparticle together with the drug. So far, nanoparticles with doxorubicin have been successfully used to treat malignant brain tumors.

An important segment of intracranial drug movement is their presence in the cerebrospinal fluid. Cerebrospinal fluid originates in the choroid plexus of the cerebral ventricles, exits through openings in the roof of the fourth cerebral ventricle, moves on the surface of the brain and enters the bloodstream via the arachnoid nodules in the upper sagittal sinus. There are about 130 milliliters of cerebrospinal fluid in total, and it is completely replaced every 4-5 hours. Medicines reach the cerebrospinal fluid relatively easily, but they leave it very quickly back into the bloodstream, because the absorption of medicines in the arachnoid nodules is many times faster than their diffusion into the brain tissue. Very little of the 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 pass easily, except for those with a high molecular weight (proteins). And the placenta behaves similarly, so we cannot practically talk about the placental barrier during pregnancy. We can count on almost any medicine we give to the mother to reach the fetus's bloodstream. When it comes to the mammary gland, it also cannot be counted on as a serious barrier to the passage of drugs. Medicines can enter milk by diffusion or active transport. Because milk is slightly acidic (rN 6.5), drugs that are weak bases tend to accumulate in milk. Drugs that bind to milk components (eg tetracyclines for calcium, liposoluble drugs for fat in milk) have a similar tendency to accumulate.

If we are talking 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 in a high percentage to plasma proteins (most often albumins) that are abundant in hydrophobic domains. A drug that is bound to a plasma protein does not exert its pharmacological effect because it is not in the vicinity of its receptor; that's why we can look at that part of the drug that is bound to albumins 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 bond with proteins, and vice versa. Medicines that are weak acids or weak bases also bind to plasma proteins. Weak acid drugs bind primarily to albumins, 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 non-specific, so that a large number of drugs can bind at the same site. This means that, when administered simultaneously, two or more drugs can displace each other from the binding site on plasma proteins, and thus change 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 we give furosemide, a Henle loop diuretic, to a patient who has been taking the anticoagulant warfarin for months, 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 anti-coagulant effect could be enhanced, which could theoretically cause bleeding in many organs in the patient (eg bleeding in the brain). However, such consequences of the mentioned 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 weak acid drugs to plasma proteins (penicillin, salicylates, barbiturates, sulfonamides) is reduced.

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

It has long been known that metals accumulate in the kidneys, which can gradually lead to the loss of the 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 of accumulation of drugs which have an affinity for the pigment of the retina called melanin. Chlorpromazine, chloroquine, ethambutol and indomethacin are such drugs, that, due to accumulation in the retina, can lead to visual impairment.

The phenomenon of redistribution

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 reach the brain capillaries in large quantities after injection (when the concentration in the blood is high), diffuse through the hematoencephalic barrier and reach a high concentration in the brain tissue. That's why their effect on the CNS occurs very quickly after administration (for example, the barbiturate thiopentone-sodium causes loss of consciousness in the patient even while it is being injected into a vein). However, when the injection is finished and a few more minutes pass, the liposoluble drugs diffuse more and more into other tissues (muscle and fat), so that their concentration in the blood drops. This has the effect that the drug now diffuses back out of 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 after 5-6 minutes of thiopentone-sodium administration). The drug actually ***moves*** from brain tissue to muscle and fat. A clinical consequence of the redistribution of thiopentone sodium is the short duration of anesthesia after its intravenous administration.

The concept of volume of distribution

Distribution volume *(V_d)* is a virtual quantity that is calculated as a quotient between the dose in which the drug was administered *(D)* and its concentration in the blood (C_p) :

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

Figure 14. Distribution of drugs in the body

It represents the volume in which the drug would be distributed under the condition that its concentration is the same in all parts of that volume, i.e. equal to the concentration of the drug in the blood. Although virtual, this size can tell us a lot about the behavior of the drug in the body. If $V_{d\,is}$ about 5 l, it can be assumed that the drug was distributed only in the intravascular space and could not leave the blood vessels (eg plasma-expander dextran 70). If $V_{d\,is}$ about 15 l, it can be assumed that the drug was distributed within the extracellular fluid (because there is about 15 l), that it is not a liposol balance and that it neither penetrates inside the cells nor into the CNS. If the volume of distribution is around 40 l , the drug has penetrated into all cells of the body ($V_{d\,is\,equal\,to\,the\,volume\,of\,total\,water\,in\,the\,body)}$, *and if* V_d is greater than 40 l (sometimes several hundred liters). It means that the drug is somewhere and deposited in the body (the largest part of the drug dose is in the depot, the concentration of the drug in the blood is low, so the ratio $D/C_{p\,is}$ high).

Biotransformation medicines

When it comes to water-soluble drugs, they are relatively easily eliminated from the body. Being mostly ionized, after filtration in the glomeruli of the kidneys 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 by freely diffusing through the membranes of the tubular cells. If nothing else happened to the liposoluble drug, once it was introduced into the body, it would remain there forever and that without the possibility of elimination. It is precisely for this reason that a defense mechanism was created during evolution that turns liposoluble substances into hydrosoluble ones and thus enables their elimination. Today, we call this mechanism of chemical change of the drug the process of biotransformation.

Biotransformation mostly takes place in the liver, on the smooth endoplasmic reticulum. There is a large number of enzymes that have very low specificity, so they can act on substrates with a very diverse chemical structure. Among them, two compounds are the most important: cytochrome P 450, which enables the insertion of an oxygen atom into the substrate molecule (thereby oxidizing it because the substrate gives up its electrons to oxygen) and cytochrome P 450-reductase, which regenerates the oxidized cytochrome P 450 and enables it to act on the next molecule substrate. That is why oxidation is the most common reaction of drug biotransformation. The oxidized drug now has an oxygen atom in its molecule that attracts electrons from the bond with the hydrogen atoms; it ends with the dissociation of a hydrogen ion that is positively charged, while the drug molecule contains oxygen that carries a negative charge. The end result is the creation of an ionized, therefore water-soluble drug. Catecholamines, neuroleptics, benzodiazepines and many other drugs are biotransformed through the process of oxidation. Although by far the largest number of drugs are oxidized under the action of cytochrome P 450, some drugs (eg, 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*** represents the introduction of electrons into the drug molecule (reduction inactivates venous vasodilators - nitrates), and ***hydrolysis*** is the splitting of the

drug molecule into two parts by the introduction of water molecules (eg hydrolysis of local anesthetics procaine, lidocaine and others).

Sometimes these basic reactions of biotransformation (oxidation, reduction and hydrolysis), which we often call the reactions of the first phase, do not lead to the creation of a sufficiently ionized drug that would be easily eliminated from the body. That being the case, it is necessary to add some polar radical to the already changed drug and increase its hydrophilicity. For this purpose, evolution has created enzymes that perform ***conjugation***, i.e. joining of altered drug molecules with polar radicals. 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 with acetic acid. We call conjugation reactions reactions of the second phase of biotransformation. Sometimes drugs do not go through first stage reactions, but are directly conjugated with radicals. An example of this behavior is the opioid analgesic morphine, which only conjugates with glucuronic acid.

Induction and inhibition of cytochrome P 450. Both the number and activity of cytochrome P 450 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 biotransformation as well as the biotransformation of other substances. Known inducers of cytochrome P 450 are pheno-barbital, carbamazepine, rifampicin, glucocorticoids, many poisons that pollute the human environment (polycyclic aromatic hydrocarbons from tobacco smoke or from grilled food, dioxin, etc.) as well as plants from the cruciferous family (cabbage, kale, cauliflower, Brussels sprouts, broccoli) and St. John's wort. Still other drugs inhibit the activity of cytochrome P 450 by binding to its chem. These are: drugs containing an imidazole group (cimetidine, ketoconazole), erythromycin, estrogen ethinyl-estradiol, spironolactone, chloramphenicol, norethindrone, anesthetic fluoroxen, solvent carbon disulfide, propylthiouracil, grapefruit juice and other substances. Whether they are cytochrome P 450 inducers or inhibitors, they can cause serious interactions with the drugs we use in practice. Inducers can speed up the metabolism of a drug that the patient takes 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 a patient with artificial heart valves who is 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 up to a toxic level. The best way to avoid such unpleasant interactions between drugs is to avoid the unnecessary administration of several drugs at the same time or, when combined therapy is absolutely necessary, to reduce or increase the dose of another drug when the first drug is an inhibitor or inducer of cytochrome P 450.

Inhibition of cytochrome P 450 can be reversible (competitive) or irreversible (so-called **suicidal inactivation)**. When the reversible inhibition is in question, after the inhibitor leaves the enzyme, the enzyme remains active. In the case of suicidal inactivation, the drug-inhibitor is metabolized by cytochrome P450 and changes 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 by the synthesis of a new enzyme. An example of a drug that performs suicidal inactivation of cytochrome P 450 is erythromycin.

There are several isoforms of cytochrome P 450 in each person, and the most abundant isoforms are CIP 3A4 (28% of the total content of P 450 in the liver), CIP 2 C 9 (20%), CIP 1A2 (12%), CIP 2E1 (6%) , CIP 2A6 (4%) and CIP 2 D 6 (4%). Some drugs are metabolized through several isoforms (eg paracetamol is metabolized via CIP 3A4, CIP 1A2 and CIP 2E1), and some only via one (eg ibuprofen via CIP 2 C 9). It is interesting that the representation of certain cytochrome P 450 isoforms changes during the development of each person. For example, the CIP 3A7 isoform appears only during fetal life and disappears after birth.

Drugs that are metabolized via multiple cytochrome isoforms are ***more suitable for clinical use*** than drugs that are metabolized via 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 through intact isoforms. Therefore, its concentration in the blood will not increase significantly. In the case of drugs that are metabolized through only one cytochrome isoform, a possible inhibition of that isoform will lead to very high concentrations of the drug in the blood and the manifestation of the toxic effects.

Inducers and inhibitors of cytochrome P 450 are most often specific for certain isoforms. According to that, to predict the effects of enzyme induction or inhibition, it is necessary to know two things: through which isoform(s) a drug is oxidized and to which isoform(s)) acts the inducer or inhibitor in question.

Excretion medicines

Excretion of drugs is the process by which drugs are expelled from the internal environment of the organism into the external environment.

Excretion of drugs through urine

The most important way of drug elimination from the body is through the kidneys. About 1200 ml of blood passes through both kidneys every minute, and about 120 ml of that is separated in the glomeruli into an ultrafiltrate that continues down the tubules. All drugs whose molecular weight is less than 60,000 daltons are filtered in the glomeruli. If they are in an ionized state, they cannot diffuse through the wall of the tubule back into the blood, but remain in the lumen of the tubule and are eliminated in the urine. First of all, the extent to which a drug will be ionized depends on its molecular structure and then on the rN of the tubular fluid. Liposoluble drugs (which have few oxygen, nitrogen or sulfur atoms in them) are minimally ionized regardless of the rN of the environment. However, most drugs are at least somewhat water-soluble, so they can be thought of as weak acids or weak bases (eg, drugs that have a COOH group are weak acids, and drugs that have an NH_2 group are weak bases). If the drug is a weak acid, it will be more ionized (dissociated) if the tubular fluid is more basic (higher rN), which means that it will be excreted more in the urine. On the other hand, if the drug is a weak base, it will be more ionized (dissociated) in acidic urine (low rN) and more excreted. By changing the rN of urine, we can increase or decrease the excretion of a drug. For example, in case of poisoning with barbiturates or acetylsalicylic acid (both drugs are weak acids), the elimination of the poison can be accelerated by the use of $NaHCO_3$, which leads to alkalinization of urine.

In addition to filtration, drugs can reach the lumen of the tubule (and thus into the urine) through the process of secretion from the tubular cells. Secretion takes place in the proximal tubule using two non-specific transport systems, located in the luminal membrane of tubulocytes. 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 anion system transports uric acid. The capacity of these secretory systems is very large, so drugs subject to tubular secretion are eliminated very quickly. An example of this is penicillin (secreted by the anionic system), where half of the administered dose is eliminated after only 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.

Medicines that are secreted can interfere with the secretion of endogenous substances and thus cause unwanted 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 anion transport system and slows down the elimination of penicillin.

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

Some natural substances and rare drugs can be actively reabsorbed in the tubules after filtration into the primary urine, e.g. glucose, amino acids and ions. Uric acid is 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, thereby increasing its excretion. On the other hand, the antituberculotic pyrazinamide blocks the tubular secretion of uric acid, thereby increasing its concentration in the blood.

Excretion of drugs through the bile

In addition to urine, drugs can also be eliminated through bile. In quantitative terms, excretion via bile is of little importance for most drugs. However, the presence of the drug in the bile may 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 through the bile can be used safely in patients with impaired kidney function. These are cardiotonic digitoxin, tetracycline and cyclin, opioid morphine and others.

Although drugs can reach the bile by diffusion, this mechanical mechanism of excretion is less significant, because it cannot concentrate the drug in the bile, whose total daily volume is not excessively large (about 1.5 l). From the hepatic sinusoids, drugs enter the hepatocytes across the basolateral membrane using transporters from the "solute carriers" superfamily.

Hepatocytes on their membrane facing the bile ducts have at least three **active transport systems**, which expel drugs into the bile. Two of the three *active biliary secretion systems* are very similar to the anion and cation tubular secretion systems in the kidney, while the third system is an unidirectional pump that expels drugs and uses an ATR (called an ATR-binding cassette, or AVS for short). Active biliary secretion systems are designed in such a way that they 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 very old people have reduced activity of the transport systems in the bile ducts. Also, liver diseases can weaken the active biliary secretion systems, and thus slow down the elimination of some drugs that damage these systems, e.g. probenecid, diethylstilbestrol and digoxin.

An additional problem with the excretion of drugs through the bile is the possibility that they will be reabsorbed in the small intestine, ie. to undergo entero-hepatic recirculation. An example of a drug that is reabsorbed in the small intestine after being excreted in the bile is the antibiotic chloramphenicol.

Excretion of drugs through the lungs

Gases and highly volatile substances are eliminated through the lungs and exhaled air. Elimination is done by simple diffusion, and there are no specialized transport systems. Anesthetic gases and vapors are taken in and eliminated through the lungs. A smaller part of ingested alcohols (ethyl alcohol, methanol, ethylene glycol) is also eliminated through the lungs. By increasing the speed and depth of respiration, the elimination of these substances can be increased to a certain extent.

Gases, vapors and other substances that are poorly soluble in the blood are quickly eliminated through the lungs (eg nitrous oxide), while highly soluble substances are eliminated very slowly (eg 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 in these ways is insignificant. The mentioned elimination routes can only be of diagnostic importance because drug concentrations in these fluids directly correlate with blood concentrations. Also, it is believed that the bitter taste that patients who receive an intravenous injection sometimes complain about comes from the rapid excretion of the drug in the saliva.

Excretion of drugs in milk

Most of the medicines taken by the mother pass into the milk. The concentration of the drug that is achieved in milk depends primarily on the concentration of the drug in the mother's blood, its liposolubility, binding to plasma proteins (high binding means weaker excretion in milk) and the existence of an active secretion mechanism. Milk is slightly acidic (rN 6.5), so drugs - weak bases - accumulate a little more in it.

Drugs with a high affinity for the milk protein lactalbumin can be concentrated in milk, as well as the liposoluble drugs that dissolve in milk fat and the drugs that act as chelating agents, i.e. bind calcium from milk (eg tetracycline antibiotics).

When the mother is taking a medicine, she should avoid breastfeeding immediately after taking the dose of medicine, because that is when the largest amount of medicine is in the milk. Medicines that are soluble in fats will be more present in the milk that the child sucks, if the feeding is in the morning and if the feeding lasts longer, because then the fat content in the milk is higher.

Pharmacokinetic parameters of drug elimination

Mathematical quantities that tell us about the speed of drug elimination from the body are clearance (Cl), elimination constant (K_e) and half-elimination time ($T_{1/2}$) . All three quantities can be calculated from the curve that describes the movement of the serum concentration of the drug in time (see figure).

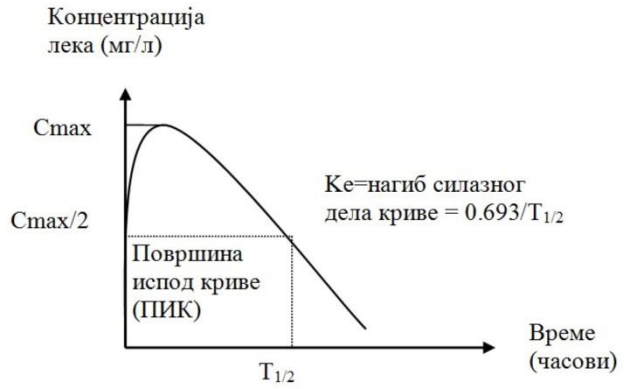


Figure 15. Drug concentration in the blood after one oral dose

Drug clearance represents the amount of blood plasma that is released from the drug in a unit of time. Total drug clearance includes all elimination routes and can be expressed as the sum of renal, hepatic, pulmonary and other clearance. It is calculated as the quotient of the total amount of the drug that is eliminated in a unit of time and the concentration of the drug in the plasma. In practice, *the total* clearance of the drug is determined from the serum drug concentration/time curve (see the picture

above), as the quotient of the drug dose and the area under the curve (PIC). If we wanted to calculate only *the renal* clearance of the drug, then we would divide the total amount of the drug that was excreted through the kidneys in a unit of time by the area under the curve. ***The half-elimination time (T $_{1/2}$)*** is the time during which half of the administered amount of the drug is eliminated from the body. In practice, the half-elimination time 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 be reduced to a 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 expressed mathematically as the tangent of the angle at which the descending part of the curve is inclined in relation to the x-axis, and is also called the elimination constant of the drug (K e). There is a simple mathematical relationship between the elimination constant (slope of the curve) and the half-elimination time: $T_{1/2} = 0.693/K_e$.

Most drugs are eliminated by the so-called ***first-order kinetics*** (or linear kinetics, which is a synonym). This means that the rate of elimination is higher if the concentration of the drug in the blood is higher. Some drugs are again metabolized by enzymes whose total number is small, i.e. the total capacity for elimination is limited. At lower concentrations in the blood, these drugs are also eliminated according to first-order kinetics; however, at higher concentrations, the enzymes that carry out the elimination are saturated so that the increase in the concentration of the drug in the blood is not accompanied by an adequate increase in the rate of elimination. For this type of elimination, we say that it is carried out according to ***saturation kinetics***. Ethanol, phenytoin, fluoxetine, acetylsalicylic acid, dicoumarol and others have saturation elimination kinetics. 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 in a unit of time - as much as the capacity of the enzymes that carry out the elimination. In this case we say that the saturation kinetics passes into the so-called zero-order kinetics.

Equilibrium state

When it comes to drugs with first-order kinetics, after repeated administration of the same dose, an equilibrium state is established in which **the amount of drug that is eliminated between two doses of the drug is equal to that dose**. After the first dose in the dosing interval, only part of it is eliminated, so that the next dose significantly increases the concentration of the drug in the blood. The increased concentration of the drug 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 concentration of the drug in the blood. Therefore, in the third dose interval an even larger part of the dose is eliminated. After 4-5 dosing intervals (provided that they are approximately equal to the elimination half-time of the drug), an equilibrium state is established. Then the concentration of the drug in the blood is maintained at a constant level, oscillating around a certain value. In practice, our goal is to give the patient the drug at regular intervals (dose intervals) to achieve an equilibrium state in which the concentration of the drug in the blood will be high enough to manifest the therapeutic effect of the drug. On the contrary, that concentration shouldn't be too high, so that toxic effects are not manifested drug effects.

The equilibrium state can be reached even faster than the 4-5 half-elimination time if we apply as the first ***shock*** dose of the drug, which is several times higher than the usual single dose (maintenance dose). We do this, for example, when we administer a shock dose of the cardiotonic digoxin, followed by maintenance doses (such a procedure is called "rapid digitalization"). When administering a shock dose, the doctor should be careful and calculate it well, because it can easily be overdone and cause serious side effects.

For successful therapy, it is very important that the patient takes his medicine 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 drops. It is necessary to pass several dosing intervals to re-establish the original equilibrium state with the desired concentration of the drug in the blood.

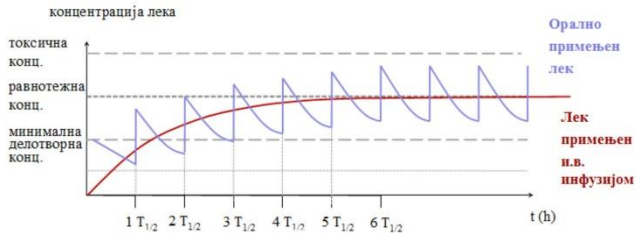


Figure 16. Establishment of the equilibrium state after chronic use of the drug

In the case of a multiple dose administration, if the dose interval is similar to $T_{1/2}$ upon establishment of the equilibrium state, the amount of drug that is eliminated between two doses is equal to the administered dose of the drug. The concentration of the drug in the blood reaches the maximum values soon after the intake of the drug, then decreases during the dose interval to the minimum (immediately before the administration of the next dose), i.e. varies around the mean, equilibrium concentration.

By correctly selecting the dose and dosing regimen, a constant mean (equilibrium) 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 the administration of drugs orally, 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 effect of the drug.

Pharmacokinetic influences are particularly numerous **in the phase of drug absorption**. Any kind of food (especially fatty food) slows down the emptying of the stomach. After eating food, it takes about 2-3 hours for it to pass into the stomach. If the patient takes the medicine immediately after a meal, it means that it will reach the small intestine for completely only after 2-3 hours, which significantly ***slows down the absorption of the medicine***. For most drugs that are used for a long time (eg months), the rate of absorption of the drug is not important; but if we want a quick effect of the drug (eg 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 medicine immediately after a meal, ie. on a full stomach, can significantly affect the degree of drug absorption. For some medicines *fat from food helps them to be absorbed better* because it stimulates the secretion of bile acids, which facilitate the dissolution of the medicine in the lumen of the small intestine and thereby increases its absorption. Other drugs *are converted by acid from the stomach into a form that is better absorbed*. The group of such drugs, which should be taken on a full stomach, include: carbamazepine, griseofulvin, saquinavir, tacrolimus, isotretinoin (due to easier dissolution), itraconazole, ketoconazole and amprenavir (due to the positive effect of the stomach acid).

There are also medicines whose food ingredients ***interfere with absorption***. Some *are not stable in an acidic environment,* so they break 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 (bonded) with metal cations* (calcium, magnesium, iron, etc.) and thus less easily absorbed, include: bisphosphonates, penicillamine, tetracyclines and quinolone antibiotics. In order to improve the absorption of such drugs, the patient should take them no later than one hour before or no earlier than 2 hours after a meal.

Certain types of food can affect **the metabolism of drugs**. Ingredients from *grapefruit juice* inhibit the metabolism and transport of some drugs before they reach the systemic circulation, thereby increasing the concentration of those 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, you should avoid consuming grapefruit juice if you are taking any of the following medications at the same time: 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 drugs that use the OATP2B1 transporter in the intestinal mucosa.

In some types of food there are ingredients that **affect the effects of medicines.** Thus, for example, food with too much protein can interfere with the passage *of levodopa* through the blood-brain barrier (because amino acids from food compete with levodopa for the transporter), which reduces the effect of levodopa on Parkinson's disease. Another classic example is food rich in tyramine (aged cheese, smoked fish and yeast), which can cause a hypertensive crisis in patients on long-term therapy with *monoamine oxidase inhibitors* (see the chapter on antidepressants). Another example is important for clinical practice: the administration of the large amounts of potassium-rich food (eg tomato juice) should be avoided in patients taking drugs that interfere with renal potassium excretion (potassium-sparing diuretics, angiotensin-converting enzyme inhibitors or angiotensin-converting enzyme receptor blockers angiotensin), because hyperkalemia is possible in the case described.

Finally, sometimes the medicine should be taken with food to avoid **irritation of the gastric mucosa** (eg non-steroidal anti-inflammatory drugs, metformin), or to prevent **the occurrence of hypoglycemia** (eg when taking oral hypoglycemic drugs).

DISEASES OF THE LIVER AND METABOLISM OF DRUGS

A large number of liver diseases disrupt its ability to metabolize drugs. The degree of weakening of the biotransformation function depends on the severity and stage of each disease. Slowed metabolism of drugs has been observed in cirrhosis, fatty degeneration of the liver, acute hepatitis of various etiology and carcinoma of liver cells. Therefore, in such conditions, all drugs

that are metabolized in the liver require a dose reduction. How much the dose should be reduced depends on the degree of liver failure caused by the patient's illness. Although there is still no adequate instrument for assessing the degree of liver failure, we use the Child-Pugh classification of stage A, B or C , where A is the mildest and C is the most severe form of liver failure. Patients are classified into these stages according to the level of 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 the dosage interval should be extended by 50%.

In cirrhosis of the liver (end stages), the greatest effect of the disease is on drugs that undergo metabolism during the first passage through the liver and are less bound to plasma proteins. Since collateral blood flow develops due to the slowed blood flow through the portal circulation (via the esophageal and anorectal veins), most of the absorbed drug bypasses the liver and reaches the systemic circulation directly. That is why the bioavailability of such drugs increases, as does their serum concentration, 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 whose characteristic is that they are metabolized very quickly in it. All conditions that reduce blood flow through the liver (eg cardiac and respiratory failure) will slow down the metabolism of such drugs (amitriptyline, imipramine, isoniazid, lidocaine, propranolol, verapamil, morphine, meperidine, pentazocine).

RENAL INSUFFICIENCY AND DRUGS

Patients who have impaired renal function face several problems when using drugs: 1) slow excretion of drugs and their metabolites; 2) they become more sensitive than other people to the effects of some drugs and 3) they have a harder time tolerating the side effects of drugs. These problems can be reduced or avoided by using smaller doses of drugs or by choosing the right drug.

It is especially important to determine the right dose of the drug for people with kidney failure: it must be neither too high nor too low. When it comes to drugs that are mostly metabolized to inactive metabolites, and then those same metabolites are only partially excreted via the kidneys, dose reduction is not necessary in renal insufficiency. This is especially true for drugs with a wide therapeutic range. On the other hand, drugs that have a narrow therapeutic range and are mostly 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 concentration of the drug in the serum.

How to use creatinine clearance to adjust the dose of drugs in renal failure? In the following way:

First of all, the fraction (F) of the drug that is excreted unchanged through the urine should be determined (for example, in the case of aminoglycosides, F=0.9, and in the case of tetracyclines, F=0.5). Then, since the renal clearance of the drug is proportional to the creatinine clearance, we need to find the ratio of creatinine clearance in a patient to whom we give the drug with a normal creatinine clearance:

Creatinine clearance $_{\text{in failure}}$ (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, in order to obtain the dose of the drug for our patient with renal insufficiency:

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

It is very important, however, that **the starting dose of the drug** (if there is any in the therapeutic regimen) in patients with renal insufficiency **is not corrected** by the mentioned factor, but remains the same as in persons with normal renal function.

In order not to calculate drug doses separately for each patient with renal insufficiency, tables with already calculated doses according to categories of renal insufficiency are usually used in practice (stage 3 - creatinine clearance 3 0-5 9 ml /min, stage 4 - creatinine clearance 1 5 -2 9 ml / min and stage 5 - creatinine clearance less than 1 5 ml / min). These tables are not completely precise, but they can satisfy the needs of the majority of patients; they can usually be found 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 the serum creatinine concentration, using the Cockroft-Gault formula:
Creatinine clearance = (140 – age) h (body weight in kg) / (72 h serum creatinine concentration)
*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. That is why sometimes the effect of orally administered drugs is absent, so the doctor has to switch to parenteral administration.

On the other hand, heart failure reduces blood flow through the liver, so 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 can be expected. A decrease in the function of cytochrome P450 oxidase also contributes to this.

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 the synthesis of prostaglandins* (non-steroidal anti-inflammatory drugs: acetylsalicylic acid, ibuprofen, diclofenac, and others), because they can further worsen the blood flow through the kidneys (which is dependent on the local synthesis of prostaglandins), and seriously damage the excretory function of the kidneys.

It is interesting that in hospital conditions an abnormal increase in aminotransferases in the serum is most often a consequence of the congestive heart failure. This been said, such a laboratory abnormality should not be immediately attributed to the drugs that the patient receives at the same time just because those drugs are metabolized in the liver.

Finally, a number of drugs can cause heart failure as a side effect. Such drugs include calcium ion 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 - lead to fluid retention and heart load), cytostatics from the anthracycline group (doxorubicin - creates free radicals that damage the myocardium), etc.

ALLERGY TO MEDICINES

Any drug can cause an allergic reaction in patients, even those used to treat allergies. Of course, some drugs do this more often (eg penicillin), and some very rarely (eg lidocaine). The drug that causes an allergy actually behaves as an antigen, either by itself or only in connection 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 recognize the drug (through specific antibodies on their membrane). Depending on the place (type of cells, tissue) to which the drug is attached and the dominant mode of reaction of the immune system (through the creation of free antibodies or T-lymphocytes), during the next contact with the drug, the body can react allergically in 4 different ways (four types of allergic reactions):

Type 1 (anaphylactic reaction)

In this type of reaction, after the first contact with the drug, the body creates IgE antibodies to the drug which bind with their Fc part to the mast cell membrane. When the drug enters the body the next time (at the earliest after 5-7 days from the first contact), it binds to IgE antibodies on mast cells and causes the degranulation of these cells. Mast cell granules release a number of mediators (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, which causes suffocation of the patient (Quinke's edema, i.e. angioedema) or bronchospasm. Milder reactions are manifested only by smallpox - urticaria (hives). Allergic reactions of the first type occur from a few minutes to a few hours after re-exposure of the patient to the drug.

An anaphylactic reaction is treated by stopping the administration of the drug that caused it and then by immediate administration of 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 N_1 and N_2 antihistamines. If the anaphylactic reaction is manifested only by hives, then it is sufficient to apply only N_1 antihistamines.

2nd type (direct cytotoxicity)

In the 2nd type of reaction, after the first introduction of the drug into the body, the immune system creates IgG or IgM antibodies to the drug. When the drug is re-introduced into the body, it binds to the membrane of a type of blood cell. Antibodies then bind to the drug and activate complement, which destroys the blood cell membrane. The result is cell lysis, ie. hemolytic anemia, leukopenia or thrombocytopenia, depending on the type of cells to which the drug is bound. The time that elapses between the patient's re-exposure to the drug and the occurrence of a type 2 allergic reaction varies greatly from patient to patient.

3rd type (formation of immune complexes)

In this type of reaction as well, the organism creates IgG or IgM antibodies, but the drug does not bind to the cell membrane. First, when the drug is repeatedly administered, the drug and 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 onset of inflammation. This type of drug allergy can manifest as serum sickness, vasculitis, measles, arthralgia, and/or fever. The third type of allergy occurs usually 1-3 weeks after the patient is re-exposed to the drug.

4th type (late hypersensitivity)

Late hypersensitivity is related to the creation of T-lymphocyte clones that recognize the drug as an antigen. Since the immune reaction of T-lymphocytes takes some time, the reaction to re-introduction of 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 local application of drugs is based on the mechanism of delayed hypersensitivity. The same mechanism causes allergic hepatitis and nephritis after the use of drugs.

Cross allergy

Medicines with similar chemical composition can cause the same allergic reaction even though only one of them has previously come into contact with the body. Due to their similar chemical structure, the immune system recognizes them as the same substance or the same antigen. That is why an allergic reaction can occur. The best-known example of cross-allergy are penicillins and cephalosporins. A person who is allergic to penicillin can also react allergically to cephalosporins (about 8-15% of patients), even though they have never received that type of antibiotic before. Namely, penicillins and cephalosporins have one identical part of the molecule - the beta-lactam ring - due to which the immune system recognizes them as the same type of antigen. Apart from penicillin, cross-allergy has also been reported between vancomycin and teicoplanin within the group of aminoglycoside antibiotics, as well as between certain non-steroidal anti-inflammatory drugs.

The most common clinical manifestations of drug allergy

Allergy to drugs is most often manifested on the skin, as *maculo-papular* measles (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 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 is always in the same place after repeated exposure to the drug (tetracyclines, sulfonamides, non-steroidal anti-inflammatory drugs, antiepileptics). In addition to the skin, internal organs can also be affected in the case of drug allergies, so that hepatitis, nephritis, hemolytic anemia, thrombocytopenia, leukopenia, or vasculitis occur. Finally, sometimes drug allergy manifests itself as a syndrome, such as: *serum sickness* (measles on the skin, arthralgia and elevated temperature, e.g. when using heterologous antibodies, infliximab, allopurinol, thiazide), *DRES syndrome* (measles on skin, elevated temperature, eosinophilia, lymphadenopathy, liver damage, e.g. with sulfonamides, allopurinol, antiepileptics) or *syndrome similar to lupus erythematosus* (e.g. with hydralazine, procainamide, isoniazid, drugs that block the effect of tumor necrosis factor alpha) .

Procedure with a patient allergic to the drug

When we determine that the patient is allergic to the drug using skin tests (prick test and intradermal test can determine the 1st type of allergy, the patch test on which the drug is applied can determine the 4th type of allergy), by measuring specific IgE antibodies in the plasma, or the Coombs test (type 2 allergy), the further use of that drug should first be stopped, and then the patient should be advised to avoid re-administration 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 drug and the patient's condition requires treatment with the drug that caused the allergy (otherwise his life will be in danger), we can continue the therapy using the *desensitization procedure*, which causes 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 using a very small volume of the highest dilution. After that, increasing volumes of the same dilution are given 4 times, with intervals of about thirty minutes. Then it is moved to the next highest dilution, and so on, until finally the full dose of the drug is administered. Temporary tolerance will last as long as drug therapy lasts, and during that time the desensitization procedure should not be repeated. If, after a certain time after stopping the therapy such a drug should be administered again, the entire desensitization procedure is repeated.

ELDERLY PERSONS AND MEDICINES

The use of medicines in the elderly (over 65 years old) has certain peculiarities that should be respected in order to avoid significant side effects. Features may be related to the pharmacokinetics or pharmacodynamics of drugs.

When it comes to **the pharmacokinetic** peculiarities of the elderly, they exist in all phases - absorption, distribution, biotransformation and excretion of drugs. In old people, the absorption of drugs is not significantly reduced in a quantitative sense; it can only be ***slowed down*** due to slowed emptying of the stomach (as a result 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, with drugs that are subject to metabolism during the first pass through the liver (eg propranolol), due to reduced blood flow through the liver in old people, the intensity of metabolism may decrease. In that case the drug reaches a higher concentration in the blood after oral administration.

The distribution of drugs in the elderly persons is affected by changes in the composition of body fluids and tissues. Adipose tissue makes up a higher 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 prolongation of their action.

The water content in the body of an elderly person is reduced by 15% on average, 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 muscles, such as, for example, digoxin. Because of this, the concentration of such drugs in the blood and their effect on target tissues increases.

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

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

Finally, the excretory capacity of the kidneys of old people is significantly reduced. Beginning at age 36, creatinine clearance declines by 1% each year; this means that, for example, 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 through the kidneys should be reduced by the percentage by which the patient turns forty. The following table lists medications whose dose should be reduced by a certain percentage in the elderly, as they are eliminated through the kidneys.

When it comes to the effect of drugs (**pharmacodynamics**), the elderly are particularly sensitive to substances with an effect on the central nervous system. Therefore, they should reduce the doses of psychotropic drugs, especially those with a sedative effect (benzodiazepines, barbiturates, tricyclic antidepressants). Medicines that otherwise have unwanted effects on the central nervous system manifest those effects more often in the elderly (eg cardiotonic glycosides more often lead to psychotic reactions in the elderly).

MEDICINES WHOSE DOSE SHOULD BE ADJUSTED IN OLD PERSONS, BECAUSE THEY ARE ELIMINATED THROUGH THE KIDNEYS		
Acyclovir	Amiloride	Captopril
Atropine	Baclofen	Ciprofloxacin
Chlorpropamide	Chloroquine	Penicillins
Enalapril	Digoxin	Tetracycline
Furosemide	Ethambutol	Cephalosporins
Methotrexate	Midazolam	Metformin
Nitrofurantoin	Ranitidine	Procainamide
Triamterene	Aminoglycosides	Thiazide diuretics

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

Adverse drug effects are more common in the elderly. Statistics show that serious side effects (those that lead to hospitalization or death) are twice as common in the elderly compared to those under 40 years of age. In particular, a higher frequency of inflammation of the large intestine was observed after the administration of antibiotics. The most likely cause of the higher frequency of side effects is the significantly higher use of drugs in the elderly.

In order to avoid unwanted and toxic effects of drugs in the elderly, doctors should adhere to certain principles in the application of drugs:

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

CHILDREN AND MEDICINES

When it comes to the administration of drugs in children, first of all, it should be understood that there are big differences in pharmacokinetics and pharmacodynamics in certain stages of the child's development. In popular terms, children are not small adults, infants (from 2 months of life to the end of 1 year) are not small children, infants (from birth to the end of 1 month) are not small infants, and premature children are not small infants. Premature children have only 10% glomerular filtration of a newborn, and the processes of glucuronidation are extremely underdeveloped. However, many functions are underdeveloped even in a newborn (glomerular filtration is only 50% of the value in adults), and only in the middle of the first year of life do they develop to a level that corresponds to the functions of an adult.

Children are especially sensitive to medicines during the first year of life, due to the slow elimination. On the other hand, from the age of 2 to 12, the clearance of drugs in children is higher than in adults, and at puberty there is a sharp decrease in clearance to the values of adults. That is why children between the ages of 2 and 12 often require higher doses of medication per kilogram of body weight than adults.

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

Intramuscular injections should not be given to prematurely born children and infants the absorption of the drug from the site of application is not predictable due to the poorly developed musculature.

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

There are specificities in the effects of some medicines in childhood. Barbiturates and antihistamines (which act as sedatives in adults) cause excitement and hyperactivity in children. Chronic phenobarbitone therapy interferes with learning and normal behavior of children; chronic corticosteroid therapy slows their growth. The use of antidepressants should be very careful in adolescents: a higher frequency of suicides than in adults using these drugs has been observed.

Due to all these specificities, doses of medicines for 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: $D_d = D_o \times TT/70$) or age of the child (Jung's formula: $D_d = D_o \times S/(S+12)$), they are not reliable enough for routine use and tend to underdose drugs. The safest way to dose is to use experienced doses for each age of the child, determined through long-term pediatric practice in most countries.

A number of medicines are contraindicated for use in children. Those are:

- tetracyclines (because they are deposited in bones and teeth during growth; teeth become yellowish, enamel is hypoplastic)
- quinolone antibiotics and uroantiseptics (pipemic acid, ciprofloxacin, olfloxacin and others are not used in people under 17 years old because they interfere with the development of joint cartilages)
- acetylsalicylic acid (in children under 8 years old 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 perform the conjugation of chloramphenicol in the liver, there may be accumulation of this drug in the body of the newborn (because it is difficult to precisely dose the drug) and damage to vital organs (kidneys, liver, heart), which manifests itself in the deadly gray ″syndrome . babies ″(anemia and cardiovascular collapse).

Some medicines in children have specific side effects, which you should be aware of:

- furosemide can cause nephrocalcinosis;
- indomethacin may cause renal failure or intestinal perforation;
- phenytoin causes thickening of the skull and coarse facial features;
- valproate can cause hepatotoxicity in children under two years of age;
- ceftriaxone in infants, it can lead to the formation of precipitates in the gallbladder (calcium-ceftriaxone), because in the bile it reaches concentrations above the limit values for the beginning of crystallization; these precipitates disappear spontaneously after discontinuation of ceftriaxone.

Many drugs 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 for children. This includes various oral forms of medicines, which are not suitable for children. Since in reality there is a need, such drugs are still given to children outside the indication area. If that is the case, then the doctor who prescribes the therapy is responsible for any possible bad consequences. Although it is primarily recommended for children to use liquid forms of drugs orally, there are dosages and tablet forms that are still given to children in the absence of liquid forms. However, there is a big difference from child to child as to whether they can swallow a tablet (no matter how small) and not to aspirate. The safest recommendations for the dosage of individual drugs in children outside the approved indications and dosage forms are found in the British book National Forms for Children. This book can be easily obtained through book importing companies or through online shopping.

DRUGS AND FEMALE GENDER

Outside the period of pregnancy, the female gender differs slightly from the male gender in the pharmacotherapeutic sense. So far, it has been observed 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 in them alcohol is very little metabolized in the stomach wall; in men, a significant part of 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 less acidity of gastric juice and that their stomach empties more slowly; also, estrogens have a dual effect on cytochromes: they reduce the activity of CIP 2 C 19 in the liver, so the metabolism of some drugs can 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 aforementioned changes in drug metabolism are much more pronounced during pregnancy, when the concentrations of estrogen in the blood are much higher.

The real specificity of women in terms of drug therapy arises during pregnancy and lactation. First of all, the conditions under which the drug moves in the body change. 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 up to 10 grams per liter. Due to the high concentration of estrogen and progesterone in the blood, there is an increase in the clearance of some drugs; 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 liver of the fetus begins to metabolize the drugs that the mother has taken into her body. Since after metabolism in the fetal liver, drugs are secreted into the amniotic fluid which is then swallowed by the fetus. There is a tendency for some drugs to accumulate in the tissues of the fetus. This has so far been demonstrated for penicillins, cephalosporins and antiretroviral drugs, but the consequences of this phenomenon are not known.

The placenta does not represent a significant barrier to the passage of drugs; practically, it can be considered that every medicine that the mother takes in also reaches the bloodstream of the fetus. During the first two weeks after fertilization, the drugs either lead to the death and elimination of the embryo or (if the embryo survives) they do not leave any consequences on the fetus. In the next 10 weeks of pregnancy (first trimester), a number of drugs (which we call teratogenic) can cause disturbances in the development of the fetus, which are manifested at birth by malformations (so-called congenital malformations). That is why these 10 weeks are the most risky period in the development of the fetus. In the second two trimesters of pregnancy, some drugs can have a toxic effect on fetal tissues and lead to minor (microscopic and functional) damage, usually to the CNS and the eye (because their development takes place throughout pregnancy). Because of all that has been said, every doctor should know which drugs can and can't be used during pregnancy. Detailed tables with recommendations for the use of drugs in pregnancy can be found in the publications of the Medicines Agency (eg in the "Pharmacotherapy Guide") or in the British National Formulary (British National Formulary - BNF), which doctors should purchase for two to three years. However, the drugs that we know today having a strong teratogenic or fetotoxic potential are: ACE inhibitors and angiotensin receptor blockers, cytostatics, antiepileptics, coumarins and lithium.

The harmful effect of drugs on the fetus is subject to certain principles: (1) there is a dependence of the harmful effect on the dose; (2) the 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 drug's mechanism of action determines what kind of disruption 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 (eg aminoglycosides) barely penetrate into milk, so they can be administered to the mother during lactation. However, most drugs pass into milk to a significant extent; many liposoluble drugs in milk reach the same concentration as in plasma (antidepressants, for example) or even concentrate in it. Given that the rN of milk is around 6.5, those drugs that are weak bases will also be concentrated in it. Medicines with a smaller volume of distribution and which are less bound to plasma proteins, pass into milk in a greater extent. Of the drugs that penetrate to a large extent into milk, the following stand out: lithium, methimazole, iodine, sotalol, atenolol and others. Detailed tables with recommendations for the use of drugs in lactation can also be found in the above-mentioned publications.

INTRODUCTION OF NEW MEDICINES IN 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 put into practice, it must go through several stages that often last for 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 drug under investigation for a long period of time in order to observe possible *chronic toxic effects* (chronic toxicity studies). Due to 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 does not belong to rodents (usually dogs or monkeys).

The 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 quickly (a new generation of bacteria emerges every 30 minutes), their cultures are exposed to the drug in order to establish its ***mutagenic potential***, i.e. 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 the animal tests have been carried out and after the approval of the independent Ethical Committee has been obtained, the clinical trials of the drugs can be started. The clinical examination is carried out in 4 phases:

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

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

3rd stage: This phase can only be accessed if the drug has shown satisfactory effectiveness in the previous phase. The drug is now given to a large number of patients who have been selected by the method of 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 (eg with the most effective drug up to that time), as well as with the natural course of the disease in the third group of patients without therapy, i.e. receives only ***placebo*** (placebo is some indifferent substance (sucrose, starch, etc.) without pharmacological effect that looks like a new drug from the outside, so patients who take it believe that they are ingesting 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 in whom we know that disease progression will occur during the study; in such cases, the new drug is compared only with the most effective drug up to that time. The comparison can be done by the so-called ***the single-blind*** method, when the doctors conducting the study know which patients are receiving the new drug and which are the old drug or placebo, while the patients do not know this. In order to achieve greater objectivity, whenever possible, the examination should be conducted according to the so-called ***double-blind*** method. In such a study, neither the doctors nor the patients know which patients are receiving the new drug during it and which old drug or which placebo is in question. Only at the end of the study are the sealed envelopes with codes that allow patients to be classified into groups opened.

Sometimes clinical studies are planned according to the principle of a "cross-over design": in the first period of the study, one group receives the drug under investigation (a new drug), and the other a placebo (or the most effective drug up to that time, the so-called active comparator). After a so-called "washout period" of several days or weeks, when the patients no longer receive any medication, a second period of the study would occur. The second period understands the group that received the new drug and that now receives a placebo. The group that was receiving a placebo is now receiving a new drug Cross-over design allows for a better assessment of drug effects and the elimination of so-called "confounding" factors that can affect the effect of drugs (eg, patient habits).

4th stage: If the drug in the 3rd phase proves to be more effective than the current treatment method, and no longer toxic, its introduction into clinical practice is prohibited. From that moment, the 4th phase of the clinical trial begins : long-term monitoring of the drug's side effects. Sometimes it is only after several years that the drug is shown to be too toxic, so it is withdrawn from use.

SPECIAL PHARMACOLOGY

AUTONOMIC NERVOUS SYSTEM

The nervous system can be divided into central (brain and spinal cord) and peripheral, which has two parts: somatic and autonomic. The somatic nervous system enables 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.

Sympathetic centers are located in the lateral horns of the spinal cord (from the 8th cervical to the 2nd lumbar segment). They are made up of so-called preganglionic neurons whose axons exit the spinal cord and reach the ganglia. 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 released. It binds to nicotinic receptors on ganglion neurons and activates them. Ganglion neurons then send their axons to peripheral organs (heart, gastrointestinal tract, etc.). At the ends of these axons, the neurotransmitter noradrenaline is released, which binds to alpha or beta receptors on the cell membrane of peripheral organs (smooth muscle cells, cells of exocrine glands, etc.). Binding to alpha or beta receptors results in activation or inhibition of these cells (for example, smooth muscle cells contract or relax, exocrine gland cells increase or decrease their secretion, etc.).

The 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 the peripheral organs. Activity initiated in sympathetic centers spreads exponentially through preganglionic and postganglionic fibers, *simultaneously activating multiple* tissues and organs.

Noradrenaline is synthesized in the endings of postganglionic nerve fibers of the sympathetic nervous system, from the amino acid tyrosine. Tyrosine enters the termination by active transport, and then in the cytosol under the action of tyrosine hydroxylase it is converted into dihydroxyphenylalanine (DOPA). DOPA is further converted into dopamine under the action of DOPA-decarboxylase. Dopamine is then taken into synaptic vesicles by active transport, where it is converted into noradrenaline under the action of dopamine-beta-hydroxylase.

When a ganglion cell of the sympathetic nervous system is activated, it sends an action potential along its axon to its termination. When the axon terminal is depolarized, calcium from the extracellular space enters the terminal, and leads to the exocytosis of noradrenaline vesicles. Noradrenaline is released into the synaptic cleft, and acts on its receptors on the postsynaptic and presynaptic membrane.

The action of noradrenaline ends due to its transfer (uptake) to the presynaptic ending (this process is called ″uptake 1 ″) or to the surrounding cells (″uptake 2 ″). Norepinephrine taken into the presynaptic ending inactivates the enzyme monoamine oxidase (MAO), and noradrenaline taken into the surrounding cells by the enzyme catechol-O-methyl transferase (COMT). MAO removes the amino group from the amine, and introduces oxygen in its place. COMT adds a methyl group to the hydroxyl group of the catechol nucleus.

Part of the sympathetic system is represented by the medulla of the adrenal gland, which we can tentatively understand as a modified sympathetic ganglion. Preganglionic sympathetic fibers that reach the adrenal medulla release acetylcholine at their terminals; acetylcholine then binds to nicotine receptors on medulla cells and activates them. The cells of the medulla respond by secreting adrenaline into the bloodstream. Since adrenaline is secreted directly into the blood, we think of it as a hormone, unlike noradrenaline, which is released from sympathetic nerve endings into the synaptic cleft, and acts as a neurotransmitter.

Adrenaline differs chemically from noradrenaline only by one more methyl group. Both compounds, as well as their precursor dopamine, have catechol (a benzene ring with two OH-groups) in their molecule, so they are called ***catecholamines***.

The parasympathetic centers are located in the cores of some cranial nerves (nn . occulomotorius , facialis , glossopharyn - gicus e t vagus) and in the lateral horns of the sacral part of the spinal cord (segments S_2-S_4). Neurons from the centers send their axons to the peripheral organs themselves (Figure 17). In the walls of peripheral organs (stomach, intestines, bronchi, urinary bladder, etc.) there are ganglion cells, with which the axons of neurons from the parasympathetic centers come into synaptic contact. At the ends of these axons, acetylcholine is secreted, which then activates nicotinic receptors on ganglion cells. Ganglion cells provide short axons that terminate on effector cells: myocardial cells, smooth muscle cells, and exocrine gland cells. At the ends of ganglion cell axons, the neurotransmitter acetylcholine is released, which then binds to muscarinic receptors on effector cells. The effect of acetylcholine on the receptors stops relatively quickly, because it is broken down by the enzyme acetylcholinesterase, which is located right next to the receptors.

Acetylcholine is synthesized in the cytoplasm of the nerve ending, from choline and acetyl-coenzyme A, under the catalytic action of choline-acetyltransferase. Synthesized acetylcholine then enters presynaptic vesicles by active transport, from where it is released after depolarization of the nerve ending and entry of calcium.

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

Acetylcholine

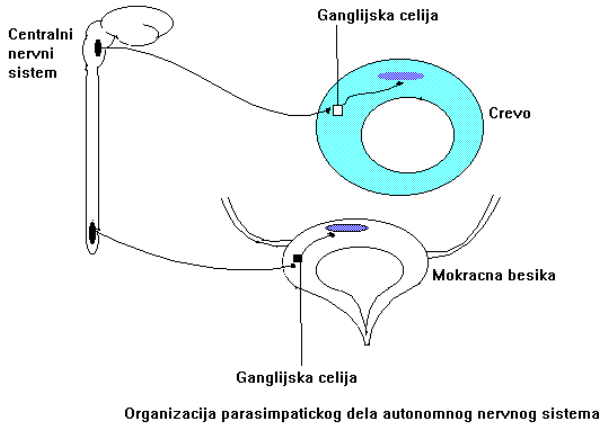


Figure 17. Parasympathetic nervous system

Nicotine receptors

Nicotinic receptors are found on ganglion cells of both the sympathetic and parasympathetic nervous systems. They belong to the group of receptor-ion channels. They got their name from nicotine, an alkaloid from tobacco, which can activate them. Under physiological conditions, they are activated by acetylcholine, which is released from the ends of preganglionic nerve fibers. The action of acetylcholine results in ganglion cell activation and impulse transmission to effector cells in peripheral organs. Nicotine receptors are also located on the cells of the adrenal medulla, where their stimulation leads to the release of adrenaline.

Localization, function and types alpha and beta receptors

Both alpha and beta receptors belong to the group of receptors linked to G-proteins. There are two basic types of alpha receptors: alpha $_1$ and alpha $_2$. Alpha $_1$ receptors are located on the smooth muscle membrane of the arteries and veins that feed the internal organs. Their activation by noradrenaline leads to an increase in the concentration of inositol triphosphate and calcium ions inside the smooth muscle cell, vasoconstriction and an increase in blood pressure. In addition, alpha $_1$ receptors are located in the bladder sphincter where their activation results in difficulty urinating. Alpha $_2$ receptors are located on the presynaptic endings of fibers of the autonomic nervous system and their activation leads to the inhibition of the adenylyl cyclase enzyme and a decrease in the release of neurotransmitters.

In some blood vessels (eg coronary arteries), in addition to alpha $_1$ receptors, there are also alpha $_2$ receptors; they are partly localized on the membrane of endothelial cells (their activation leads to the release of nitric oxide, which then relaxes the smooth muscle cells in the artery wall, i.e. causes vasodilation), and partly on the smooth muscle cells, which contract when activated by noradrenaline and lead to vasoconstriction.

In the gastrointestinal tract, alpha $_1$ receptors are located on the smooth muscle cells of the sphincter; their activation leads to the contraction of the sphincter. Alpha $_2$ receptors are present on ganglion cells, where they reduce the release of acetylcholine, thereby inhibiting peristalsis.

Less significant roles of the alpha $_1$ receptor are related to the contraction of m. dilator pupillae (and consequent expansion of the pupil), strengthening of the heart muscle contraction force, acceleration of glucose metabolism, contraction of the internal sphincter of the urinary bladder and contraction of the m.erector pili (resulting in hair loss).

There are three subtypes of alpha 1 receptors (A, B, and D) and three subtypes of alpha $_2$ receptors (A, B, and C). Of the alpha 2 receptor subtypes, only the B subtype can be found on the postsynaptic membrane.

Beta receptors exist in three forms: beta $_1$, beta $_2$ and beta $_3$. All of these receptor forms are associated with stimulation of the intracellular enzyme adenylyl cyclase, which generates cAMP from ATP. Beta $_1$ receptors are located in the heart and on the cells of the juxtaglomerular apparatus of the kidneys; their activation leads to an acceleration of the heart, an increase in the force of contraction, an increase in conduction speed and an increase in the excitability of heart cells. Activation of the beta $_1$ receptor in the kidney leads to an increase in the secretion of renin, which results in an increase in blood pressure. Beta $_2$ receptors are located on the smooth muscle cells of the bronchi, where they lead to relaxation and bronchodilation. In addition, there are them on the muscle of the uterus, bladder (they relax them) and in the blood vessels that feed the extremities (they lead to vasodilation). Beta $_3$ receptors are found on fat tissue cells; their activation is accompanied by an increase in the intensity of lipolysis.

beta $_2$ receptors on striated muscle cells, where they increase the entry of potassium ions into the sarcoplasm. On liver cells, beta $_2$ receptors activate the process of glycogenolysis, which results in an increase in glycemia. Also, a smaller number of beta $_2$ receptors are found in the myocardium, where, like beta $_1$ receptors, they increase the force of contraction.

Insulin secretion from pancreatic endocrine cells is stimulated by beta receptors and inhibited by alpha $_2$ receptors.

Receptors parasympathetic nervous system

On effector cells of peripheral organs (heart, gastrointestinal tract, bronchi, urinary bladder, etc.) there are muscarinic receptors activated by acetylcholine. Muscarinic receptors belong to the group of receptors linked to G-proteins. They got their name from the alkaloid of the Amanita muscaria mushroom, muscarine, which activates them. There are 5 types of muscarinic receptors (M_1, M_2, M_3, M_4, M_5). Stimulation of **M_1, M_3 and M_5** receptors increases the concentration of inositol-triphosphate and diacyl-glycerol in the cytoplasm (which leads to an increase in the concentration of calcium in the cytoplasm), and activates adenylate cyclase, while stimulation of **M_2 and M_4** receptors inhibits the activity of adenylate cyclase (stimulation of M_2 receptors additionally opens channels for potassium ions). 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 under the influence of acetylcholine leads to an increase in the secretion of hydrochloric acid and to the contraction of smooth muscles. M_2 receptors are primarily found in the heart, where their stimulation leads to a slowing of the heart's work, a decrease in the force of cardiac contraction, a slowing of conduction and a decrease in the excitability of heart cells. Apart from the heart, M_2 receptors are found in the brain and autonomic ganglia. M_3 receptors are located on smooth muscle cells of the respiratory, gastrointestinal and genitourinary tracts; their stimulation leads to contraction. Apart from smooth muscle cells, M_3 receptors are found on exocrine glands, in the brain and on endothelial cells. M_4 receptors are present in the brain and on autonomic ganglia, and M_5 receptors only in the brain.

Clinically significant medicines which one they act across sympathetic nervous system

Medicines that mimic the effects of activation of the sympathetic nervous system are called ***sympathomimetics***. They can act directly on alpha and beta receptors and then 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 terminals, or inhibit its release from the synaptic cleft. Amphetamine causes the release of norepinephrine from the nerve endings, and due to this action causes tachycardia and hypertension. Since it penetrates through the hematoencephalic barrier into the CNS, it also has central stimulatory effects: euphoria, loss of appetite, increased alertness, and in toxic doses, convulsions. Ephedrine acts similarly to amphetamine; only its effect is significantly longer because it is metabolized more slowly.

Ephedrine is known for losing its effect after one day of use, i.e. to empty noradrenaline depots from nerve endings. This type of tolerance, which occurs quickly (in 1 day), is called ***tachyphylaxis***.

Cocaine blocks the process of uptake of noradrenaline into the presynaptic terminal ("uptake 1") and thus leads to the accumulation of noradrenaline near the receptor. In addition, it blocks Na^+ channels in the neuron membrane and thus prevents the transmission of impulses along the axon. Because of these effects, it was used as a surface local anesthetic in otorhinolaryngology and ophthalmology: it successfully anesthetizes the mucous membrane and leads to its decongestion due to the 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 α and β receptors are ***direct sympathomimetics***. According to their chemical structure, they can be classified into 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 created in the adrenal medulla, by methylation of noradrenaline. It belongs to catecholamines activating αandβ receptors, but the effect on β-receptors is more pronounced. It leads to stimulation of the heart (increased strength of contraction, increase in heart rate, increase in conduction velocity in the heart and increase in irritability), vasodilatation in skeletal muscles (β_2-effect**)** and vasoconstriction in the skin and internal organs (α_1-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 physiological solution in a ratio of 1:10). Since adrenaline acts as a bronchodilator by activating β_2**-** receptors, it can be used to treat asthma attacks. Adrenaline is added in a small amount to solutions of local anesthetics in order to slow down their resorption from the site of application and thereby prolong their effect.

When applying adrenaline, you should know that it is metabolized extremely quickly. Therefore, the effect of the applied dose passes quickly which means that already after 10-20 minutes a new dose should be given!

Agonists α are also direct sympathomimetics. Among the natural substances, the catecholamine noradrenaline has the highest affinity for α**- receptors.** However, it is not completely selective: it activates β-receptors to a lesser extent. Noradrenaline increases the strength of myocardial contraction (increasing oxygen consumption) by direct action on the heart and increases both systolic and diastolic arterial blood pressure by acting on alpha1 receptors on the 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, the baroreceptors are activated, so that parasympathetic fibers for the heart are activated by reflex, causing the heart to slow down, i.e. bradycardia.

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

Although phenylephrine, naphazoline and xylometazoline very effectively cause vasoconstriction and decongestion of the nasal mucosa, reactive hyperemia of the nasal mucosa occurs and the congestion becomes even greater than before the application of these drugs in the form of nasal drops. This drives the patient to reach for the drops again, and conditions are created for the creation of a vicious circle, i.e. "circle vitiosus"- a . Patients should be warned to use the nasal drops as little as possible and in as little a dose as possible.

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

α. -receptor blockers. Blockers αcan block both α_1 and α_2 receptors (phentolamine, phenoxybenzamine) or only α_1 (prazosin, terazosin, doxazosin, tamsulosin, urapidil) or α_2 receptors (yohimbine). α_2 selective blocker yohimbine is not used in medical practice, but it is abused due to its stimulating effects on the central nervous system (irritability, increased motor activity, tremors) 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). In the blood of a patient with this tumor, there is a large concentration of adrenaline and noradrenaline, which is why the patient has extremely high blood pressure that can lead to bleeding in the brain. Intravenous administration of phentolamine can quickly (but short-term) control blood pressure and reduce it to normal values. It is used during surgical intervention to remove the tumor (one hour before surgery, 10 mg of phentolamine is administered intravenously). During a longer period of time, while preparing for surgery, the patient can take phenoxybenzamine orally (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 α-receptors. Phentolamine and phenoxybenzamine are not used for the treatment of essential hypertension because they have an extremely undesirable effect - reflex tachycardia. Both drugs lead to a pronounced 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. This difficulty is partially overcome by the α_1 -selective blockers prazosin and terazosin. Prazosin does not block presynaptic α_2 receptors, so a high level of released noradrenaline due to blockade of postsynaptic α_1 receptors freely activates α_2 receptors and inhibits further release of noradrenaline. As a result, reflex tachycardia is much less pronounced than with non-selective αβ-blockers.

In addition to the selective blockade of alpha $_1$ receptors, prazosin acts directly as a vasodilator in higher dozes: in the smooth muscle cells of blood vessels, 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 $\alpha_{the\ 1}$ -receptor in the muscle capsule of the prostate leads to relaxation, prazosin facilitates urination in patients with prostate hypertrophy. Both prazosin and other selective α_1 -blockers can be used for symptomatic treatment of obstruction in prostatic hypertrophy; by blocking the alpha $_1$ receptor in the internal sphincter of the urethra, they facilitate urination. Especially useful for this indication is tamsulosin, which selectively blocks alpha $_{1A}$ receptors (which dominate in the internal sphincter of the urethra), while its effect is much smaller on alpha $_{1B}$ receptors, dominant on the smooth muscle cells of blood vessels.

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

And prazosin can cause postural hypotension as an unwanted effect (the phenomenon that when taking an upright position, blood pressure further decreases and due to reduced brain perfusion, the patient feels dizzy and unsteady. In the rare cases, the loss of consciousness can also occur), but it occurs much less often and in a milder form than in the cases of using phenoxybenzamine or phentolamine. Postural hypotension occurs much more often if the patient has a sodium deficit (eg, with dehydration, long-term use of diuretics or long-term salt-free diet).

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

Receptor βagonists. βcan be non-selective (they activate both β_1, β_2 and β_3 receptors: isoprenaline and orciprenaline), they can activate only β_1 (dobutamine) or only β_2 receptors (salbutamol, fenoterol, hexoprenaline, ritodrine). Non-selective β-agonists were

once widely used for the treatment of asthma attacks because by stimulating β_2 receptors on the smooth muscles of the bronchi, they lead to broncho-dilation. However, due to their non-selectivity, they also activate β_1 receptors located in the heart, leading to its stimulation (speeding up the heart's work, increasing the force of cardiac contraction, accelerating conduction and increasing the excitability of heart cells). Stimulation of the heart requires greater oxygen consumption in the myocardium, which should be met by increased blood flow through the coronary arteries. If the patient has narrowed coronary arteries due to atherosclerosis, ischemia and even necrosis of the myocardium may occur after the administration of isoprenaline or orciprenaline. Because of this side effect, non-selective ββ-agonists are now rarely used for this indication; their place in the treatment of asthma has been taken by selective β_2 agonists, in which the stimulation of the heart is much less pronounced (but still there!). Salbutamol and fenoterol can be administered by inhalation (aerosol) or orally. In practice, two other selective agonists, ritodrine and hexoprenaline , have also found wide application β. They have a special affinity for β_2 receptors located in the myometrium. By stimulating these receptors, they cause relaxation of the uterus, especially in pregnancy (tocolitic effect). Such an effect is of great importance for preventing and suppressing premature contractions of the uterus during pregnancy; ritodrine or hexoprenaline can stop threatened miscarriage and delay preterm labor. They are administered orally or intravenously. The oral dose of ritodrine is 10 mg /4-6 hours, and the intravenous dose is 0.15-0.3 mg /min, until the end of uterine contractions. Today, it is considered useless to apply tocolytics for longer than 72 hours; if uterine contractions do not stop during this time, further administration of tocolytics is also ineffective. The only thing that patients get when using tocolytics for more than 72 hours are unpleasant side effects: palpitations and tremors.

In addition to unwanted stimulation of the heart, all β**agonists** cause tremors at rest (which can sometimes interfere with normal activities), nervousness, dizziness, and nausea.

Dobutamine, as a selective beta $_1$-receptor agonist, is used today to treat ***cardiogenic shock*** . Its advantage over dopamine lies in the fact that it increases the consumption of oxygen in the myocardium less, so there is less possibility that myocardial hypoxemia will occur due to strong stimulation of the heart. 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-elimination time of dobutamine is only 2 minutes, because it is very quickly broken down by catechol-o-methyltransferase in the liver.

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

Non-selective β-blockers (propranolol, pindolol) reduce the work of the heart (reduce the force of contraction, decrease the frequency, speed of conduction and irritability), have an antiarrhythmic effect and lead to a decrease in blood pressure. The hypotensive effect is also contributed by reduced production of renin in the juxtaglomerular cells of the kidneys, which are normally controlled by β_1-receptors **.** The hypotensive effect is not manifested immediately after the administration of the drug (acute), because there is a reflex increase in the peripheral resistance to blood flow. However, gradually the peripheral resistance decreases, so the effect **of chronic** administration of these drugs is a lowering of blood pressure. Apart from being antiarrhythmics and antihypertensives, these drugs are also used in the treatment of angina pectoris; although beta-blockers reduce the blood flow through the coronary arteries (which could have a harmful effect in angina pectoris), they much more reduce the overall work of the heart and thus the consumption of oxygen in the myocardium, which has a positive effect. Clinical studies have shown that the use of ββ-blockers after myocardial infarction significantly reduces the risk of re-infarction.

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

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

In addition to all the above, beta-blockers have several other indications for use. Because they reduce the production of aqueous humor in the ciliary body, beta-blockers are successfully used in glaucoma, especially chronic. For this indication, timolol and betaxolol are used in the form of eye drops. Beta-blockers can also suppress peripheral manifestations of anxiety (palpitations, tremors) and 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 (eg calcium channel blockers) should be avoided. Due to the blockade of β_2**-** receptors in the blood vessels of the extremities (which normally cause vasodilatation after stimulation), worsening of ischemic disease can occur, and due to the blockade of β_2-receptors on liver cells, the release of glucose from hepatocytes under the influence of adrenaline is prevented. Because glycogenolysis in the liver is important for the correction of hypoglycemia, especially in diabetic patients receiving insulin, beta-blockers should be used very cautiously in diabetics, otherwise they may worsen hypoglycemia and increase ***its*** deleterious effect on the central nervous system. On the other hand, beta-blockers also reduce the secretion of insulin from the beta cells of the pancreas, and interfere with

the entry of glucose into muscle tissue cells. The overall result of the influence of beta-blockers on glucose metabolism is a tendency towards hyperglycemia and the onset or worsening of diabetes.

In addition to the above, in persons with severe, but still compensated heart failure, blockade βof -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 β_2-receptors in the bronchi can lead to bronchospasm.

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

In an attempt to avoid these side effects, drugs were synthesized that selectively block only β_1-receptors: atenolol, carvedilol, bisoprolol, metoprolol and others. However, their selectivity is not absolute - and they (though less often) can cause the same side effects. Another attempt to avoid side effects was the synthesis βof -blockers that are partial agonists, i.e. besides blocking the effect of endogenous catecholamines on β-receptors, they also activate these receptors to some extent. However, the clinical application of these drugs (pindolol, alprenolol) did not confirm this assumption, so their advantage over classic beta-blockers has not been proven.

Propranolol is metabolized in the liver quickly, already on the first passage. That's why its oral dose is 10 times higher than intravenous! It is highly liposoluble, so it penetrates the CNS and sometimes causes unwanted central effects (nightmares, depression, confusion). Metoprolol, a selective beta $_1$-blocker, behaves similarly. Bisoprolol is the most widely used in practice among selective beta $_1$ -blockers, because it practically does not penetrate the central nervous system and has so-called balanced elimination, i.e. and is metabolized by the liver, and is 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 beta $_1$-blocker with partial agonist activity, has a bioavailability of about 50% after oral administration. It is metabolized in the liver to an active metabolite.

A very special beta-blocker is esmolol, selective for beta $_1$-receptors, which breaks down extremely quickly: the half-elimination time is only 9 minutes. **Esmolol** is broken down 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. At the same time, its beta-blocking effect is 3 times weaker than propranolol, and its alpha-blocking effect is 10 times weaker than phentolamine. Labe-talol is also a partial beta-receptor agonist, and it also has a stabilizing effect on membranes. In addition to all the mentioned effects, labetalol can block the reuptake of noradrenaline and dopamine in the nerve endings, which sometimes paradoxically causes a jump in blood pressure at the first application.

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

Labetalol summarily reduces peripheral resistance to blood flow and lowers blood pressure, with a minimal reduction in heart rate, significantly less than after administration 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, lebetalol is very similar to ***carvedilol*** , a drug with a combined alpha and beta blocking effect, 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, the enzyme that converts tyrosine to DOPA. It is used for preoperative preparation as well as for the treatment of pheochromocytoma patients (if they cannot be operated on for any reason).

Alkaloids different principal

The ryegrass fungus that parasitizes rye and other cereals synthesizes a large number of pharmacologically active substances that belong to the group of alkaloids (that is, they show a basic reaction). Although some authors classify ryegrass alkaloids as alpha blockers, their action is complex and is the result 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 arterio-venous connections in the neck; both effects result in better blood circulation and oxygenation of the head. That's why ergotamine is successfully used to stop migraine attacks (one 2 mg lingual tablet should be placed under the tongue as soon as possible from the onset of the attack). Ergometrine and its semi-synthetic derivative methyl-ergometrine (the dose is 0.2 mg intramuscularly) have a strong spasmogenic effect on the uterus in addition to the vasoconstrictor effect: they cause a prolonged, tonic contraction of the uterus, which reduces 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 must not 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 preparations is vasoconstriction on the extremities and an increase in blood pressure. In the Middle Ages, poisoning by bread made from rye with a lot of bran was very common. In poisoned patients, due to intense vasoconstriction, necrosis of the distal parts of the extremities would occur, which would turn black and look as if they had been burned (hence the name "St. Anthony's fire"). As among the alkaloids of ryegrass and lysergic acid diethylamide (LSD), the poisoned had hallucinations and went into delirium. The strange behavior of the "witches" who were later burned at the stake is thought to be attributable to ryegrass alkaloid poisoning!

If two hydrogens are added to the alkaloids of ryegrass, dihydrogenated derivatives are obtained that behave differently; some of them get an alpha-blocker effect, so they cause vasodilation! Dihydroergotoxin is such an ergotoxin derivative; it is used for the treatment of hypertension and senile dementia due to arteriosclerosis (however, its effectiveness is very low, so it will most likely be taken out of use soon, i.e. declared an obsolete drug).

Dopamine

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 smaller concentrations acts only on its specific dopamine receptors in the arteries of the kidney, myocardium, brain and mesentery, causing vasodilation. Activation of D_1 dopamine receptors (located on blood vessels) leads to vasodilation, increased diuresis and increased sodium excretion. Activation of D_2 dopamine receptors (located on ganglion cells, adrenal cortex, sympathetic nerve endings and in the cardiovascular center in the medulla oblongata) leads to bradycardia, hypotension and vasodilatation in the kidney.

In higher concentrations, dopamine increases the release of noradrenaline, and stimulates β_1 receptors in the heart (causing an acceleration of the heart's work, an increase in contraction, an acceleration of conduction and an increase in excitability). Then the systolic blood pressure rises, while the diastolic pressure remains the same.

In very high concentrations, dopamine activates α_1 receptors in blood vessels (causing vasoconstriction). There is an increase in both systolic and diastolic blood pressure.

If administered carefully (in lower doses, 5-10 μg / kg / min), dopamine is extremely useful for the treatment of ***shock*** because it stimulates the heart and maintains blood flow through the kidneys, preventing the onset of acute renal failure.

Clinically significant medicines which one they act across parasympathetic system

Nicotine. Nicotine is an alkaloid found in the tobacco leaf. It binds to nicotine receptors, which it first activates and then blocks (because it leads to a permanent depolarization of the cell, which can no longer respond to new stimuli). The effect of nicotine introduced into the body by smoking represents the sum of the effects of activation of the vegetative ganglia and central effects. Due to the activation of the sympathetic ganglia, there is an acceleration of the heart and a jump in blood pressure. Due to the activation of the parasympathetic ganglia, there is an increase in the secretion of the exocrine glands and an acceleration of the motility of the digestive tract.

By acting on the central nervous system, it improves memory, reduces aggressiveness, 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 used to tobacco, nicotine can induce vomiting by directly stimulating the vomiting center in the brainstem. In higher doses, nicotine can cause tremors and convulsions.

Small doses of nicotine stimulate breathing through the activation of chemoreceptors in special corpuscles, which are located near the arch of the aorta and the carotid sinus. In higher doses, nicotine also stimulates breathing, but with a direct effect on the respiratory center.

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

Nicotine is a lipophilic substance, which is easily absorbed from the site of application, and penetrates through the hematoencephalic and placental barriers (from inhaled tobacco smoke, 98% of nicotine is absorbed!). 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 (eg pilocarpine) and synthetic choline esters: methanechol, bethanechol and carbachol. All these substances act on muscarinic receptors as well as acetylcholine, but are more resistant to the action of acetylcholinesterase; they can be used clinically because their effect lasts long enough (the effect of acetylcholine lasts only a few minutes). While pilocarpine, methacholine and bethanechol are selective muscarinic receptor agonists, carbachol activates both nicotinic and muscarinic receptors.

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

After systemic administration in smaller doses, choline esters cause vasodilation, drop in blood pressure and reflex tachycardia (due to baroreceptor activation). In larger doses, their direct effect on M_2 receptors in the S A and AV node 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 easier urination.

Bethanechol is sometimes used to stimulate intestinal peristalsis in patients with paralytic ileus, and to prevent urinary retention after pelvic surgery. Methacholine is only of diagnostic importance: its application via inhalation can detect patients with asthma, because excessive bronchoconstriction occurs in them (*metacholine test*). Pilocarpine is used in ophthalmology to treat acute glaucoma. After local application to the conjunctiva, pilocarpine is absorbed and leads to contraction of the ciliary muscle and pupillary sphincter.

Acetylcholinesterase inhibitors. By blocking the enzyme acetylcholinesterase, the breakdown of acetylcholine is prevented and it accumulates in the synaptic cleft, near its receptors. Thus, the receptors are stimulated longer and more strongly, so clinically significant effects are manifested. In healthy individuals, they are reflected in the signs of stimulation of the parasympathetic nervous system (acceleration of peristalsis in the digestive tract, increased secretion of exocrine glands, bronchoconstriction, miosis, spasm of accommodation, sweating) and the central nervous system, but only on the condition that the cholinesterase blocker passes through the blood-brain barrier (in therapeutic doses a slight increase in alertness and in toxic doses leads to convulsions, then coma and paralysis of the respiratory center). Initially, fasciculations are seen on the muscles and that is when paralysis occurs, due to *desensitization* of nicotine receptors under the constant action of acetylcholine (desensitization: receptor activation no longer produces the same effect in the cell).

Acetyl-cholinesterase blockers are more selective in their action than direct cholinomimetics, because they activate muscarinic and nicotinic receptors ***only in active*** cholinergic synapses. They also do not stimulate muscarinic receptors on endothelial cells, because 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 importance. **Quaternary ammonium compounds** (edrophonium and ambenonium) bind to the anionic site on the enzyme, to which acetylcholine normally binds, and thus competitively prevent the degradation of acetylcholine. The effect of edrophonium lasts only 5-10 minutes, while ambenonium lasts for 4-8 hours. Both of these drugs have a certain direct agonistic effect on nicotinic receptors. **Carbamates** (carbamic acid esters: neostigmine, physostigmine, pyridostigmine, rivastigmine) carbamylate the esterase site on the enzyme acetylcholinesterase and inactivate it; the carbamino radical is then *slowly* spontaneously hydrolyzed from the esterase site, so that the enzyme becomes active again. **Organophosphates** (insecticides parathion and malathion, isofluorophate, echothiophate, nerve warfare poisons sarin, soman, tabun and veix) perform irreversible inactivation of the esterase site of acetylcholinesterase, by covalently binding to that site. **Inhibitors of acetylcholinesterase in the central nervous system** (tacrine, donepezil, alkaloid zelenkade galantamine) are chemically diverse compounds, which somewhat specifically reversibly inhibit acetylcholinesterase in the CNS.

Quaternary ammonium compounds (edrophonium, ambenonium, but also neostigmine and pyridostigmine) do not penetrate through the hematoencephalic barrier, but are absorbed well enough 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). Organo-phosphates are very liposoluble, so they can be absorbed in a high percentage through the skin. Both carbamates and organophosphates are broken down by hydrolysis in the blood and many organs, and their metabolites are excreted in the urine.

Because of their effect on peristalsis, some of these drugs (neostigmine, for example) are used to treat paralytic ileus. These drugs have a much greater therapeutic significance in situations where neuromuscular transmission is weakened, 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 more efficiently activates the remaining nicotinic receptors. 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.

Tacrine, donepezil, rivastigmine and galantamine are used to treat Alzheimer's dementia, a neurodegenerative disease characterized by progressive loss of memory and cognitive function. The effect of these drugs is small, and is reduced to a temporary (several months) improvement in symptoms; they do not affect the progression of the disease. Tacrine is no longer used today, due to its pronounced hepatotoxicity.

Physostigmine is used topically, in the form of eye drops, in the treatment of open-angle glaucoma. Organophosphates echothiophate and demecarium were previously used for the same purposes, but today their use is limited, because they can cause ***cataracts*** after long-term use.

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 action**, because then it almost certainly causes convulsions in the patient.

Cholinesterase blockers are widely used as insecticides and, unfortunately, as warfare agents. These are compounds from the carbamate group (eg carbaryl) that reversibly block acetylcholinesterase and compounds from the organophosphate group (insecticides: parathion, malathion; war poisons: sarin, soman, tabun, veix) that block this enzyme irreversibly. Due to heavy use, poisoning with these substances is 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 the use ***of atropine*** (in individual doses of 1 mg until the clinical signs of excessive stimulation of the parasympathetic nerves disappear) which blocks muscarinic effects and ***oxime*** (eg pralidoxime) which unblocks acetylcholinesterase and enables it to function normally. Oximes are all the more effective if they are applied earlier, because over time the covalent bond between the poison and the enzyme "ages", so the drug is no longer able to break it. Since pralidoxime is a quaternary ammonium compound, it does not penetrate the CNS, so it cannot unblock acetylcholinesterase in central synapses. The dose of pralidoxime is 1-2 g, intramuscularly or intravenously. Oximes are beneficial only in organophosphate poisoning; in the case of carbamate poisoning, the effect is zero.

When people poisoned by organophosphates receive treatment (atropine and pralidoxime), their condition improves quickly, but it is necessary to remain hospitalized for the next few days. The reason for this is the possibility of redistribution of the poison, which moves from the fat 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 organophosphate poisoning.

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

Blockers of muscarinic receptors. The alkaloids from nightshade and tatula, atropine and scopolamine, competitively block muscarinic receptors and cause effects opposite to parasympathetic activation: tachycardia, relaxation of the gastro-intestinal muscles, difficulty urinating, mydriasis and paralysis of accommodation, bronchodilation, reduction of secretion of salivary and bronchial glands. In addition, they penetrate the CNS and cause first amnesia, impaired concentration and sleepiness, and later confusion, ataxia, asynergia, delirium and very rarely coma (a set of these symptoms is called "central anticholinergic syndrome"). Due to the blocking of muscarinic receptors in the vestibular nuclei and the vomiting center, they prevent vomiting while driving (kinetosis) if they are taken before setting off on the road. Anticholinergic drugs do not significantly affect the blood vessels (except for slight redness of the face and upper chest), because the muscarinic receptors on the 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 highly 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 of general anesthesia because it reduces secretion in the bronchial tree. Atropine can also be used to diagnose S A node dysfunction in the heart: if sinus bradycardia is due to extracardiac causes, atropine will speed up the heartbeat, and if the problem is in the S A node itself, there will be no change. And people with syncope due to carotid sinus hypersensitivity can benefit from taking atropine, which prevents extreme reflex bradycardia. Scopolamine is applied transdermally, using a patch from which it is absorbed through the skin (thanks to its high liposolubility); prevents vomiting due to driving, but only if the patch is applied before starting the journey.

Atropine and scopolamine are well absorbed and easily penetrate into 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 that block muscarinic receptors such as scopolamine and atropine have been found. Some of them penetrate well into the CNS, so they are used in situations where it is desirable to reduce the activity of cholinergic pathways. One such drug is trihexyphenidyl, which is used in the treatment of Parkinson's disease (in this disease, the dopaminergic nigrostriatal pathways that normally maintain a balance with the cholinergic striatonigral pathways are damaged; the latter becomes overactive). 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 therapy of spasms of the smooth muscles of the ureter (renal colic), intestine (intestinal colic) and biliary tract (biliary colic). Such drugs are scopolamine-butyl bromide and propantheline.

A special group of anticholinergic drugs consists of oxybutynin, dicyclomine and tolterodine, which are used to reduce the reactivity of the bladder, i.e. in the case of uninhibited bladder, bladder spasm, nocturnal urination and incontinence. Tolterodine acts selectively on muscarinic receptors in the urinary bladder to some extent.

Due to their pharmacological effect, muscarinic receptor blockers must not be used in people with glaucoma (an eye disease caused by increased intraocular pressure) and in elderly men with difficulty urinating due to prostate hypertrophy. In glaucoma, these drugs further increase intraocular pressure, and in prostate hypertrophy, they can cause the patient to stop urinating completely (urine retention). In elderly people, anticholinergic drugs can weaken memory.

Stimulants and blockers nicotine receptors on the ganglion cells (the so- called ganglion stimulators and blockers)

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

On the other hand, the use of drugs that only block nicotinic receptors (mecamylamine, hexamethonium, trimethaphan) immediately leads to the interruption of the activity of both the sympathetic and parasympathetic parts of the vegetative system. The main effects in the body are: tachycardia, orthostatic hypotension / hypotension that occurs when the patient moves from a sitting position to a standing position; due to ganglion blockade, the baroreceptor reflex does not function/, urine retention, constipation, decreased saliva secretion, mydriasis and cycloplegia. Given the low selectivity of nicotinic receptor blockers (hexamethonium, mecamylamine, etc.), they are rarely used in practice. The only clinical application found is the ganglion blocker trimethaphan, which is used to cause controlled hypotension during neurosurgical interventions. The extremely short half-elimination time of trimethaphan (measured in minutes) allows precise control of blood pressure by simply regulating the rate of intravenous infusion.

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

PHARMACOLOGY OF THE EYE

Medicines in the eye 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 narrowing of the pupil (miosis), spasm of the ciliary muscle and accelerated swelling of the aqueous humor through the angle between the iris and the cornea (and thus to a decrease in pressure). Activation of sympathetic fibers causes dilation of the pupil (mydriasis) and an increase in the production of aqueous humor in the ciliary body through the action of β_2-receptors (thereby increasing the pressure of aqueous humor).

When we want to examine the fundus or measure the refractive ability of the eye (eg to determine the diopter) it is necessary to expand the pupil and relax the ciliary muscle (so that the lens bulges as much as possible). We will achieve this by using muscarinic receptor blockers in drops: atropine, homatropine or tropicamide. Homatropin and tropi-kamide act much shorter than atropine, whose effect can last for a week! We can expand the pupil (but without affecting the ciliary muscle) by using the αphenylephrine receptor agonist.

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 (synechia) between the iris and the cornea or ciliary body. Since the blood flow in the eye is accelerated during inflammation, atropine is quickly absorbed, so its effect lasts only a few hours instead of 7 days. Thus, by applying atropine 3 times a day, the tendon expands and contracts the same number of times during the day: we jokingly call it "gymnastics of the tendon".

Glaucoma is an eye disease characterized by pain and damage to the retina due to increased pressure of the aqueous humor. In acute glaucoma (so-called closed-angle glaucoma), the cause of a sudden increase in the pressure of the aqueous humor is the approach of the iris to the cornea, which makes it difficult to drain the aqueous humor. Then the muscarinic receptor agonist should be applied urgently in drops, which will lead to miosis and contraction of the ciliary muscle, separate the iris from the cornea and ease the swelling of the 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 accumulation of acetylcholine on the receptors.

Chronic glaucoma (so-called open-angle glaucoma) is most likely due to an increased production of aqueous humor, as a result of which its pressure is permanently elevated. The drugs of choice for chronic glaucoma are $_2$-receptor blockers β**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, because otherwise there may be unwanted effects on the lungs and heart (bronchospasm and bradycardia).

The agonist of alpha 2 adrenergic receptors, **brimonidine**, lowers intraocular pressure by a double effect: it reduces the production of aqueous humor on the ciliary body and increases swelling through an increase in uveoscleral blood flow. Brimonidine alone can lower intraocular pressure by 23 to 27% compared to pretreatment values. It is applied locally, in the form of eye drops.

Dorzolamide and brinzolamide, carbonic anhydrase inhibitors, are used to reduce the production of aqueous humor. Dorzolamide is administered locally, in the form of eye drops (20 mg / ml), three times a day; can lower intraocular pressure by 5 mmHg . Unfortunately, it causes conjunctivitis in about 7% of patients. Brinzolamide is also administered as eye drops; side effects cause 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 are intolerant of other medications. These are synthetic analogs of prostaglandin $F_{2\alpha}$, **latanoprost, bimatoprost and travoprost**. They are applied in the form of eye drops, they diffuse through the cornea into the interior of the eye and there they are broken down to the active form. They increase the swelling of the aqueous humor by a still unknown mechanism. They are used once a day and are somewhat more effective than timolol and betaxolol. Adverse effects of latanoprost are conjunctivitis (10% of patients) and iris discoloration (7% of patients). After instillation into the eye, bimatoprost begins to work in 4 hours, and its effect lasts for even 24 hours. Compared to latanoprost, bimatoprost causes greater hyperemia of the conjunctiva and pigmentation of the iris.

Ripasudil is the one that has appeared and which acts as an inhibitor of the Rho kinase ROCK. Rho are proteins that bind GTP (whose substrate is Rho kinases ROCK 1 and 2) and are enzymes that through several intermediate reactions ultimately lead to the polymerization of actin fibers. Due to the inhibition of 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. That's how 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 efficiency, the maximum lowering of intraocular pressure does not lag behind other anti-glaucoma drugs. Of the side effects, only hyperemia of the testicles has been recorded so far. Similar to ripasudil is **netarsudil**, which in addition to inhibiting Rho kinase ROCK blocks the uptake of noradrenaline; it is also used as an eye drop to treat chronic glaucoma, and causes hyperemia of the orbit as a major side effect.

EICOSANOIDS

Eicosanoids are substances that are formed from polyunsaturated fatty acids with 20 carbon atoms, and especially from arachidonic acid (Greek εικοσι= twenty). Under the action of phospholipase A_2, arachidonic acid is released from the phospholipids of cell membranes. Three enzymes can further act on free arachidonic acid :

1. cyclooxygenase , which catalyzes occurrence prostaglandins , thromboxane (TXA_2) and _ _ prostacyclin ;
2. lipoxygenase , which catalyzes occurrence trihydroxy - and cositetraenoic acid (lipoxins, LX_A and LX_B) or leukotrienes (LTB_4 , LTC_4 , LTD_4 and LTE_4).
3. cytochrome P 450 reductase , which catalyzes occurrence epok sid (5,6- oxido -, 8,9- oxido -, 11,12- oxido - and 14,15- oxido - icositetraenoic acid)

Effects on tissues. Eicosanoids act on membrane receptors that are linked to G-proteins. Prostaglandins E and F have the most pronounced effects. $PG\ E_2$ and $PG\ E_1$ act on a large number of smooth muscles: they dilate blood vessels, contract the longitudinal and relax the circular muscles of the digestive tract, contract the smooth muscle of the uterus and relax the smooth muscles of the bronchi. $PG\ E_1$ and $PG\ E_2$ raise body temperature and increase the release of pituitary hormones (growth hormone, TSH , ACTH , FSH and LH). $PGF_{2\alpha}$ and TXA_2 act vasoconstrictor (mainly on veins) and bronchoconstrictor. $PGF_{2\alpha}$ contracts the smooth muscles of the digestive tract and uterus.

TXA_2 promotes platelet aggregation, while prostacyclin (PGI_2) inhibits aggregation and causes vasodilation.

LTB_4 is an extremely strong chemotactic agent for neutrophils. LTC_4 and LTD_4 are powerful bronchoconstrictors, causing increased capillary permeability and increased secretion of mucus in the bronchial glands. Leukotrienes are thought to be the main mediators that play a role in the development of bronchial asthma (they used to be collectively called "slow-reacting substance").

$L\ X_A$ and $L\ X_B$ inhibit the cytotoxicity of natural killer cells and act chemotactically.

Indications for the use of eicosanoids. $PG\ E_2$ and $PGF_{2\alpha}$ are used to prepare the cervix of the uterus for abortion, as well as to induce abortion in the first and second trimesters of pregnancy.

PGI_2 (epoprostenol) is used to treat pulmonary hypertension, and $PG\ E_1$ and PGI_2 to treat Raynaud's syndrome and peripheral arteriosclerosis.

$PG\ E_1$ is used to maintain an open ductus arterio-zus in newborns before surgical intervention on the heart (for transposition of large arteries, pulmonary atresia, etc.).

Misoprostol (an analogue of $PG\ E_1$) is used for the prevention and treatment of stomach ulcers caused by the use of non-steroidal anti-inflammatory drugs. It has a cytoprotective effect, and in larger doses it reduces the secretion of HCl.

$PG\ E_2$ and PGI_2 are used to prevent organ rejection in transplants because they inhibit the proliferation of T and B lymphocytes.

Adverse effects of prostaglandins represent an extension of their pharmacological effects. They most often cause nausea, vomiting and diarrhea. Prostaglandin E_1 causes hypotension, flushing and headache. $PGF_{2\alpha}$ in higher doses can cause severe pulmonary hypertension or a spike in blood pressure in the systemic circulation.

HISTAMINE AND ANTIHISTAMINICS

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 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 a neurotransmitter in the central nervous system.

Histamine can be released from the cells in which it is deposited in **two** ways: ***by the effect of antigens*** on the 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 cells that contain histamine, or lead to the release of histamine from the granules. Medicines and other substances that can lead to the release of histamine by a non-exocytotic mechanism are: morphine, codeine, guanethidine, d-tubocurarine, iodine contrast agents, bradykinin, neurotensin, somatostatin, substance P, polymyxin B, anaphylatoxins from complement and basic polypeptides and phospholipase A from insect venom.

When released, histamine exhibits the following effects: vasodilatation (arterioles, capillaries and venules), increased permeability of capillaries, edema, redness of the skin, itching, contraction of the smooth muscles of the respiratory tract, gastrointestinal and genitourinary tracts. All the mentioned effects are achieved by histamine through the activation of the N_1 receptor. In addition to N_1 receptors, there are N_2 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, N_1 receptors are important for maintaining wakefulness, and both N_1 and N_2 receptors participate in the regulation of blood pressure, body temperature, fluid homeostasis and the processing of pain sensations. In recent years, the existence of both N_3 and N_4 histamine receptors has been demonstrated. All types of histamine receptors, from 1 to 4, belong to the superfamily of receptors linked to G-proteins; N_1 receptors lead to the mobilization of calcium through phospholipase S, N_2 receptors increase the concentration of cAMP, and N_3 and N_4 receptors reduce the entry of calcium into neurons, because they close the neuronal type of channels for calcium in the membrane. N_3 receptors are located at the ends of sympathetic nerve trains 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 a person comes into contact with them, histamine can penetrate the body and cause its effects.

For now, drugs that competitively block N_1 and N_2 receptors have found clinical application. N_1 antihistamines are mainly used for their anti-allergic effect. There are two generations of N_1 antihistamines. Drugs from ***the first generation*** are **ethanolamine derivatives (diphenhydramine, dimenhydrinate), ethylenediamine** derivatives (pyrylamine, tripelenamine), **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-elimination time is usually 4-6 hours. N_1 antihistamines of the first generation block vasodilation caused by histamine, reduce the permeability of capillaries and the sensation of itching (reduce the stimulation of nerve endings). Due to the passage into the CNS, they cause sedation. Many of the first-generation antihistamines have an antimuscarinic effect; phenothiazines also block alpha adrenergic receptors, and cyproheptadine also blocks serotonin receptors. The most important side effects of $N1_{\text{antihistamines}}$ of the first generation are **sedation** and **antimuscarinic** effects (dry mouth, constipation, urine retention, paralysis of accommodation). In the case of poisoning (taking doses of antihistamines many times higher than recommended), symptoms similar to atropine poisoning occur: initially excitement, hallucinations, dry mouth, mydriasis, facial redness, urine retention, tachycardia, and later convulsions and coma. N_1 antihistamines of the first generation alleviate the symptoms of allergic reactions (allergic rhinitis, urticaria, anaphylactic reactions), can prevent the occurrence of motion sickness, have a beneficial symptomatic effect in Meniere's syndrome (dizziness due to an increase in endolymph pressure in the semicircular canals) and can be used as hypnotics.

N_1 antihistamines ***of the second generation*** are water-soluble drugs, piperidine derivatives, which poorly penetrate the CNS and cause very weak sedation. Loratadine, desloratadine, cetirizine and fexofenadine are eliminated relatively slowly, so their effects last up to 24 hours. Loratadine and desloratadine are metabolized in the liver by cytochrome CIP 3A4, while cetirizine and fexofenadine are not metabolized, but are excreted unchanged in the urine (cetirizine) and feces (fexofenadine). These drugs block vasodilatation caused by histamine, reduce the permeability of capillaries and the sensation of itching (reduce the stimulation of nerve endings). In addition, antihistamines of the second generation inhibit the release of a large number of inflammatory mediators, by a mechanism that does not involve blockade of the N_1 receptor. Therefore, in addition to the treatment of 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. Terfenadine and astemizole used to be included in group $N_{1\text{ of second-generation antihistamines;}}$ however, these two drugs blocked myocardial potassium (K+) ion channels, prolonged the QT interval on the EKG, and caused potentially fatal ventricular tachycardia, *torsades de points*. This was especially pronounced in people who took other drugs, inhibitors of cytochrome CIP 3A4, due to which there was a jump in the concentration of terfenadine or astemizole in the plasma. Today, terfenadine and astemizole are **banned** for use in many countries.

Apart from the indications already mentioned, N_1 antihistamines are also used for the treatment of more severe forms of vomiting in the 1st trimester of pregnancy (hyperemesis gravidarum). The basis for this application of $N1_{\text{blockers}}$ is the existence of functional $N1_{\text{receptors}}$ in the vomiting center (see the chapter "Emetics").

N_2 receptor blockers (cimetidine, ranitidine, famo-tidine) are used to treat peptic ulcer (see chapter on peptic ulcer therapy), gastro-oesophageal reflux and Colinger-Ellison syndrome (hypersecretion of stomach acid due to tumors of endocrine cells of the pancreas that secrete gastrin). These drugs are also used in the treatment of anaphylactic reaction, together with N_1 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 in the form of inhalation to prevent attacks of bronchial asthma, and in the form of drops for the nose and eyes, for the treatment of 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 (called raphe , hypothalamus, pituitary gland, limbic system) and peripheral nervous system, where it performs the function of a neurotransmitter. However, the largest part of serotonin can be found in the endocrine (argentafine) cells of the mucosa of the gastrointestinal tract (90%) and platelets (6%). It is metabolized by the action of mono-aminooxidase and aldehyde dehydrogenase to 5-hydroxyindoleacetic acid.

Serotonin causes contraction of the smooth muscles of the digestive tract, vasodilatation in skeletal muscles and the heart, vasoconstriction in other organs, thickening of the endocardium in the right half of the heart, increased aggregation of platelets, and stimulation of pain sensory nerve endings and chemo-sensitive vagal afferent fibers in the coronary circ. -lation. This amine achieves its effects through specific receptors of which there are 7 types: 5-NT_1, 5-NT_2, 5-NT_3, 5-NT_4, 5-NT_5, 5-NT_6 and 5-NT_7. A number of these types are actually a set of several subtypes of receptors that are designated by the letters: A, B, C, D and E (for example 5-NT_{1A}, 5-NT_{1D}, etc.). The 5-NT_1 receptor has 5 subtypes, and the 5-NT_2 receptor has 3 subtypes.

Serotonin itself has no therapeutic application, but some agonists and antagonists of certain subtypes of its receptors are clinically very useful. The 5- $HT_{1D\ receptor}$ agonist, **sumatriptan,** has shown excellent efficacy in interrupting migraine attacks. Subcutaneous administration of 6 mg of sumatriptan stops migraine attacks in up to 70% of patients. Apart from sumatriptan, drugs with the same mechanism of action and effect came into use: **zolmitriptan, naratriptan, rizatriptan and almatriptan**. All are used to stop migraine attacks, while only sumatriptan is also 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-$_{HT\,1A}$ agonist, shows an anxiolytic effect without causing sedation.

Medicines that block 5- HT_2 receptors have an antipsychotic effect, ie. belong to the so-called atypical antipsychotics: **quetiapine, aripiprazole, ziprasidone and olanzapine**.

Tegaserod is a partial agonist of the 5 HT_4 receptor; acting on that subtype of serotonin receptors on sensory neurons causes the release of other neurotransmitters (eg calcitonin gene-related peptide). In the digestive tract, tegaserod stimulates peristalsis, increases secretion and inhibits the sensitivity of the intestinal wall. It has proven to be effective in the treatment of irritable bowel syndrome in women dominated by constipation. The main side effect of tegaserod is diarrhea.

On the other hand, 5- HT_3 receptor blockers, **ondansetron and granisetron are** used as antiemetics when using cytostatics. They are especially effective if administered immediately before cytostatic therapy - they completely prevent acute vomiting. The non-selective 5- HT receptor blocker, **cipro-ptadine,** also blocks H_1 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 Billrot 2 gastric resection, and cold urticaria.

CENTRAL NERVOUS SYSTEM (CNS) PHARMACOLOGY

NEUROTRANSMITTERS IN THE CNS

The millions of neurons that make up the central nervous system communicate with each other through neurotransmitters. The 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 it is converted into dihydroxyphenylalanine (DOPA). DOPA is further converted into dopamine under the action of DOPA-decarboxylase. Dopamine is released at its terminals by neurons classified in well-defined pathways (dopaminergic pathways). *The nigro-striatal pathway* (neuron bodies are in the s. nigra and axon endings in the corpus striatum) is important for the basic control of movements within the extrapyramidal system. Its damage leads to the appearance of Parkinson's disease (muscle rigidity, hypokinesia and tremors). *Meso-limbic* and *meso-cortical* dopaminergic pathways (neuron bodies are in the mesencephalon and their axons end in the limbic system, i.e. 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 lobe of the pituitary gland. Dopamine binds to its specific receptors in the CNS, of which there are five subtypes (D_1, D_2, D_3, D_4 and D_5). All dopamine receptor subtypes belong to the G-protein coupled receptor superfamily. After acting on the receptors, dopamine (like other catecholamine noradrenaline) is taken into the nerve endings and surrounding cells, where it is broken down under the action of monoamine oxidase (MAO, especially type MAO-B) and catechol-O-methyl transferase (COMT).

Noradrenaline. Noradrenaline is another catecholamine with neurotransmitter properties in the CNS. The largest number of noradrenaline-containing neurons 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 decreased in patients with major depression and increased in anxious states. Nor-adrenaline binds mainly to α-receptors in the CNS, but there are also functional beta-receptors. Noradrenaline plays a significant role in the processes of learning, memory and 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 action of acetylcholine) have been shown to improve conditions in Alzheimer's dementia. Acetylcholine binds to nicotinic and muscarinic receptors in the CNS.

Serotonin (5-hydroxytryptamine). Serotonin is a mediator of neurons whose bodies are located in the raphe nuclei, the central structure of the pons and mesencephalon. Their axons extend to almost all parts of the CNS, where they mainly exert an inhibitory effect. Serotonergic pathways are thought to regulate the circadian 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 release from the nerve endings, serotonin binds to specific serotonin receptors (there are 7 subtypes of these receptors). Its effect ceases due to uptake into nerve endings and metabolism under the action of monoamine oxidase.

Amino acids like 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 endings of excitatory neurons and prevents the release of their transmitters. GABA binds to its GABA-A receptors (these are channels for chlorine ions) or to GABA-B receptors (receptors linked to G-proteins that affect the opening of channels for potassium ions), leading to the opening of ion channels and hyperpolarization membranes. GABA-A receptors consist of 5 subunits that bridge the cell membrane, between which there is a channel for chlorine ions. Hyperpolarized nerve endings cannot release their vesicle-deposited transmitters. Medicines that potentiate the effect 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 taken up again in the nerve endings. It is inactivated in the cytoplasm under the action of GABA-transaminase.

GABA receptors can be blocked by bicuculline, an alkaloid of plant origin that causes convulsions in humans, picrotoxin, and pentylenetetrazol. 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 mostly found in the spinal cord, and according to their role, they belong to interneurons. They reduce the activity of neurons that participate in the reflex arc of spinal reflexes. That is why the blockade of glycine receptors with strychnine leads to convulsions and tetanic contractions of the 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 performed with the help of these neurotransmitters. Glutamate and aspartate bind to two types of receptors: *ionotropic* (belonging to the ion channel receptor superfamily) and *metabotropic* (belonging to the G-protein coupled receptor superfamily). 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 A MPA 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. Via ionotropic receptors, glutamate and aspartate cause rapid effects in the cells they act on (within a few milliseconds), and via 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 neuro-transmitter role has not yet been proven. ***Substance P*** (a peptide of 11 amino acids) is a neurotransmitter in Edinger's spino-thalamic pathway that transmits pain information (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 the concentration of cupstance P in the substantia nigra decreases in the neurological disease Huntington's chorea. ***Vasopressin*** and ***oxytocin***, two nona-peptides, are found in nerve endings in the neurohypophysis. They act as both neurotransmitters and hormones. As neurotransmitters, they inhibit neurons in the neurohypophysis; the physiological significance of that inhibition is unknown. As hormones, they act on distant organs. Oxytocin contracts the smooth muscle cells of the uterus and the myoepithelial cells of the mammary glands, and relaxes the smooth muscle cells of the fallopian tubes. Vasopressin (another name is antidiuretic hormone) facilitates the absorption of water in the collecting ducts of the kidneys and contracts the blood vessels of the gastrointestinal tract.

Endogenous opioid peptides were also discovered in the brain, which bind to opioid receptors (mi, kappa and delta). They are produced 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 experience of pain.

Blood-brain barrier

Between the blood and neurons in the CNS there is a barrier that drugs and endogenous substances must cross in order to reach the neurons from the blood. We call that barrier the blood-brain barrier. It consists of endothelial cells of brain capillaries and extensions of such astrocytes, which surround the capillaries. Endothelial cells of these capillaries are firmly connected to each other and have no pores, so substances from the blood must pass THROUGH the endothelial cells to reach the neurons.

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

In some parts of the brain, the blood-brain barrier is not intact (capillaries are permeable), which allows neurons to directly "feel" the presence of certain substances in the blood. These areas are the chemoreceptor zone in the area postremi (under the floor of the 4th ventricle), the preoptic recess and parts of the floor of the 3rd cerebral 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 in that 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 that activity more or less. In small doses they only lead to sedation while in larger doses they cause drowsiness and sleep, and in toxic doses they induce the patient into a comatose state. They are given to patients who are anxious, usually for a short period of time

(7-10 days). Longer application is not desirable, because the patient gets used to it and becomes dependent, and his basic problem - the cause of anxiety - is not solved.

Today, the most commonly used sedatives ***are benzodiazepines***. They got their name from their chemical structure: the skeleton of the molecule consists 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 GABA receptor opening - chlorine channels); thereby leading to increased inhibition and depression of CNS activity. Since benzodiazepines bind to a different place on the GABA receptor than GABA itself, and affect the binding of GABA on 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 have the opposite effect of benzodiazepines: they make the action of GABA more difficult. Because of this action, we call beta-carbolines inverse agonists, which cause anxiety and convulsions in experimental animals.

The first benzodiazepine to come into widespread use was chlordiazepoxide. So far, more than 2000 benzodiazepines have been synthesized, of which thirty are used as medicines. Diazepam, lorazepam, bromazepam, alprazolam, clonazepam and midazolam are mostly used here. Benzodiazepines are fairly safe drugs to administer - even in very large, toxic doses they rarely lead to complete CNS depression and death. However, if they are taken together with alcohol or another sedative, the depressant effect is summed up and a fatal outcome can occur. The specific antidote for benzodiazepine poisoning is *flumazenil*, a drug that blocks the benzodiazepine receptor.

Benzodiazepines reduce anxiety, but they also make patients sluggish and sleepy. Higher doses lead to relaxation of the 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 so much that breathing or heartbeat stops. Due to such a large therapeutic range, i.e. safety, benzodiazepines are the sedatives of choice today.

The main indications for the use of benzodiazepines are patient restlessness (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 essential difference between benzodiazepines in terms of sedative effect, but when it comes to hypnotic effect (inducing sleep), nitrazepam, flu-razepam and temazepam are used the most. In addition to sedatives, diazepam and lorazepam are used to interrupt 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 cause the so-called "conscious sedation", i.e. calming down the patient during these unpleasant examinations. In addition, midazolam (like all other benzodiazepines) causes ***anterograde amnesia*** (the person who receives it does not later remember what happened in the next hour or two), so the patient agrees to repeated examinations.

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

The use of benzodiazepines should be avoided during pregnancy: teratogenic effects have been described! The most common side effects of benzodiazepines are drowsiness, poor motor coordination, confusion and memory loss. Hallucinations, blurred vision, paradoxical excitation and gastrointestinal complaints occur less often.

Benzodiazepines are metabolized in the liver; most are first oxidized to cytochromes and then conjugated to glucuronic acid. Exceptions to this rule are lorazepam, which is directly conjugated, and clonazepam, which is directly acetylated. According to the length 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) medium-acting - lorazepam, clonazepam, alprazolam, temazepam; and (3) short-acting - midazolam and triazolam.

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

Tolerance develops to benzodiazepines and patients become psychologically and physically *dependent* after prolonged use of these drugs. If you suddenly stop taking benzodiazepines, a withdrawal syndrome occurs, which consists of the following symptoms: insomnia, anxiety, tremors, muscle weakness, nausea, hyperalgesia and convulsions (they rarely occur). Withdrawal syndrome can be prevented if the patient is first transferred to equivalent doses of diazepam (because its half-elimination time is long), and then the daily dose is reduced by about 10 to 20% per week, until the administration is stopped completely.

In order to avoid the development of tolerance and dependence on benzodiazepines, it is recommended that patients do not use them for longer than 4 weeks when it comes to the treatment of insomnia, or no longer than 8 weeks when it comes to the treatment of 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 appearance of benzodiazepines, the most commonly 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 effect of GABA, but in a different way. They work ***by increasing the time*** that the chlorine 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 large enough dose, they lead to depression and the lowest parts of the CNS (cardiovascular and respiratory center) and death. Barbiturate poisonings (suicidal and homicidal) are otherwise very common. There is no antidote, but measures are used to support the work of the heart and lungs (infusions of physiological solutions, artificial ventilation).

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

Barbiturates are metabolized in the liver, first by oxidation on cytochromes and then by conjugation. According to the length 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.

Unwanted effects of barbiturates are excessive sedation, depression, weakening of thinking and memory processes, then the appearance of nystagmus, ataxia (cerebellar symptoms) and addiction (physical and psychological). 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 (heme synthesis disorder) because they accelerate the formation of toxic heme precursors.

Apart from benzodiazepines and barbiturates, other substances also show sedative and hypnotic effects: chloral hydrate, meprobamate, glutethimide, etchlorvinol and others. However, as they have more side effects and do not have any advantages compared to benzodiazepines and barbiturates, they are used extremely rarely.

Two drugs, which have a different chemical composition 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 are somewhat different from those of benzodiazepines. They cause sedation and hypnosis, but have anxiolytic, muscle relaxant and anticonvulsant effects, weaker than benzodiazepines. Due to their short effect, these drugs are used as hypnotics, especially for insomniacs who have trouble falling asleep. Patients have no problems with hangovers the next day. The half-elimination time of zaleplon is only 1 hour, zolpidem 2-3 hours and zopiclone 5 hours.

Pure anxiolytics separate the sedative effect from the anxiolytic one. **Buspirone** is one of the relatively new drugs that has been shown to have an anxiolytic effect without causing sedation. It binds to serotonin receptors of type 5- NT_{1A} (on which it acts as a partial agonist), and in order to manifest its effect, at least a week should pass from the start of administration. Buspirone also has no muscle relaxant or anticonvulsant effects.

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 around 70 kg)

SEDATIVE	INDICATION	METHOD OF APPLICATION	SINGLE DOSE	GET IT INTERVAL
Diazepam	Status epilepticus	Intravenous injection (i.v.)	10 mg	The same dose can be repeated after 30-60 minutes
Diazepam	Anxiety	orally	2 mg	8 hours
Nitrazepam	Insomnia	orally	5 mg	One dose at bedtime
Midazolam	"Conscious Sedation"	i.v.	2 mg	After 2 minutes, add 0.5 mg, if needed

CENTRAL NERVOUS SYSTEM STIMULANTS

Stimulation of the central nervous system includes *increased alertness, the appearance of anxiety and, if it is particularly strong, convulsions*. Stimulation can occur in three basic ways: depression of inhibitory neurotransmission in the CNS, enhancement of excitatory neurotransmission or removal of presynaptic control of neurotransmitter release. Medicines 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, pentylenetetrazole 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 closing of the chlorine channel and depolarization of the neuron membrane. Strychnine works in another way: it blocks receptors for the inhibitory neurotransmitter glycine, which are especially present in the spinal cord and medulla oblongata. Inhibition of glycine receptors enables 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 from this group are well absorbed after oral administration, and have a short-term effect, because they are quickly 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 when fully conscious, he actually suffocates. 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 removing catecholamines from presynaptic terminals, preventing their reuptake, and stimulating dopamine and serotonin receptors.

These drugs are well absorbed after oral administration, 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 urine.

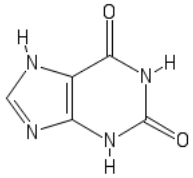
Amphetamine, pemoline and methylphenidate are used to treat *hyperkinetic syndrome* in children (hyperactivity, impulsive behavior and inability to concentrate). Amphetamine is also effective in the treatment of *narcolepsy* (a disorder characterized by daytime sleep attacks, sudden loss of muscle tone - cataplexy, nightmares and flaccid paralysis upon awakening). Modafinil, whose mechanism of action is unknown, is also successfully used to treat narcolepsy.

If these drugs are overdosed, euphoria, tremors, heart stimulation, irritability, insomnia, and then convulsions and coma occur. Chronic administration of psychomotor stimulants leads to weight loss due to anorexia and psychosis-like conditions.

Psychomotor stimulants cause psychological and physical dependence. Tolerance develops towards them. When the long-term use of amphetamines is abruptly stopped, a withdrawal syndrome occurs, consisting of the following symptoms: long-term 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 core.

Three methylxanthines have pharmacological significance: caffeine, theophylline and theobromine. Caffeine is found in coffee (one cup of coffee has about 100 mg of caffeine), tea (30 mg per cup of tea), cocoa (a cup of hot cocoa has 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 $_{\text{receptors}}$ for adenosine, thus preventing the inhibitory effect of adenosine on both the postsynaptic and presynaptic membranes. In addition, caffeine also acts as an inverse agonist of benzodiazepine receptors, thus reducing the permeability of chloride ion channels. All these effects ultimately lead to the depolarization of the neuron membrane and their excitation.

Methylxanthines are used to treat intoxication with CNS depressors: a combination of caffeine and sodium benzoate is administered intramuscularly. Theophylline is used to stop attacks of bronchial asthma, in the form of an 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 citrate salt is used for the short-term treatment of apnea in premature babies. When aminophylline is administered as an intravenous injection, it must last at least 20 minutes. If it is administered faster, there is a risk of arrhythmias.

Caffeine is also effective in combination with non-opioid analgesics to stop headaches, because it causes vasoconstriction of the blood vessels of the brain.

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

Addiction can develop to caffeine from coffee. People who drink more than 6 cups of coffee a day become addicted to caffeine, so that if they do not take the usual dose, they get a severe headache and a feeling of fatigue.

ANTIPSYCHOTICS

The name **"psychosis"** means a disorder that can have different causes, but must have the following symptomatology: hallucinations, illusions, reduced ability to process information and draw logical conclusions, catatonia, inappropriate behavior, aggression and loss of associations. Schizophrenia is a type of psychosis, which is characterized by a chronic course, loss of emotions, withdrawal and the feeling of losing control over one's thoughts. Schizophrenia symptoms can be divided into " *positive* ", which actually represent an abnormal enhancement of normal functions (eg agitation), and " *negative* ", which represent a loss of normal functions (eg, loss of emotions). Negative symptoms are far more resistant to therapy.

It is believed that the biochemical basis of schizophrenia is the increased activity of dopaminergic nerve pathways: meso-limbic and meso-cortical. Antipsychotics primarily block dopamine receptors on neurons where dopaminergic pathways terminate (all block the D_2 receptor subtype). However, blockade of dopamine D_4 and 5-HT_2 serotonin receptors also contributes to the antipsychotic effect. In addition to the mentioned receptors, a number of antipsychotics also block muscarinic, alpha-adrenergic and H_1 histaminergic receptors.

Antipsychotics are drugs that are used to treat schizophrenia, the manic phase of manic-depressive psychosis and some delirious states. Antipsychotics are divided into 4 chemical classes: **phenothiazines** (which are divided into *aliphatic* compounds - chlorpromazine, *piperidines* - thioridazine, and *piperazines* - flufe-nazine), **butyrophenones** (haloperidol), **thioxanthenes** (thiothic-sen) and others, so-called. " **atypical** " or "new" drugs. $_{Atypical}$ antipsychotics (clozapine, olanzapine, risperidone and its active metabolite paliperidone, quetiapine, ziprasidone, aripiprazole, asenapine) in addition to binding to D_2 dopamine receptors, can block D_4 receptors and serotonin receptors, especially the 5- HT 2 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: occurrence of crazy ideas, illusions and hallucinations, agitation. "Negative" symptoms of schizophrenia (weak socialization, emotional dullness, deficit in the thinking process), unfortunately, respond poorly to these drugs. In order for the full effect of antipsychotics to manifest, several days, even weeks, should pass. About 40% of patients respond poorly to "typical" antipsychotics; they are indicated for the use of clozapine, which is currently considered the most effective antipsychotic.

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: a syndrome similar to Parkinson's disease (akinesia, rigidity and tremor), acute dystonia (curvature of the neck, head, face), akathisia (attacks of hypermotility) and tardive dyskinesia (appearance of choreiform movements -that after several months of therapy) due to blockade of the nigro-striatal pathway. The secretion of milk (galactorrhoea), amenorrhea, gynecomastia and the loss of libido in men while increased libido in women appear due to blockage of the tubero-infundibular pathway and increased secretion of prolactin. Antipsychotics also block muscarinic receptors, so they often exhibit unwanted anticholinergic effects, such as: constipation, difficulty urinating, dry mouth, difficulty sweating, accommodation disorder. To some extent, these drugs also block α-adrenergic receptors, which leads to postural hypotension and inability to ejaculate. Antipsychotics also lower the hypothalamic thermostat resulting in hypothermia. By an as yet unknown mechanism, they cause heart rhythm disturbances (especially thioridazine, which causes prolongation of the QT interval), have an epileptogenic effect and, in a small number of patients, cause hepatitis followed by jaundice. A rare but very serious side effect of antipsychotics is the so-called neuroleptic malignant syndrome. It is characterized by muscular rigor, an increase in body temperature and hypotension with a tendency to go into a shock state. It is treated primarily by stopping the use of 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 H_1 histaminergic receptors, many antipsychotics (especially phenothiazines) cause sedation, which is why one daily dose of the drug is taken in the evening before going to bed.

Antipsychotics cause photosensitisation, and can deposit in the cornea, lens and retina (thioridazine can also cause retinopathy).

Clozapine has a special 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 side effects from typical ones. While typical antipsychotics are dominated by motor disorders and side effects due to blocking of other receptors of the autonomic nervous system, these effects are much less pronounced with atypical ones. However, atypical antipsychotics have pronounced **metabolic** side effects: in patients there is an increase in body weight (except for aripiprazole), hyperlipidemia, reduced glucose tolerance, hyperglycemia, and even the onset of diabetes. Of all

atypical antipsychotics, clozapine and olanzapine have the most pronounced metabolic side effects, while aripiprazole (does not cause weight gain and hyperlipidemia) and ziprasidone have the least.

Antipsychotics have another beneficial effect: they prevent vomiting. Together with the opioid analgesic fentanyl, haloperidol is used to induce the so-called neurolept-analgesia in which it is possible to perform shorter surgical interventions or unpleasant diagnostic procedures; an antipsychotic reduces the patient's emotional response to pain.

Choice of antipsychotics

Although there are some clinical studies that claim that atypical antipsychotics are more effective than classic ("typical"), there is still not enough evidence to make a definitive statement. It is characteristic of antipsychotics that their effect is very individual: one patient responds well to some 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 suits him best 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 unwanted effects, especially when the patient already has an additional disease, such as metabolic syndrome or prolactinoma. Of the atypical antipsychotics, quetiapine has the least tendency to cause extrapyramidal syndrome, and risperidone and paliperidone have the highest tendency 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 antipsychotic therapy. Multiple antipsychotics should never be combined, as this does not increase effectiveness. Antipsychotics can usually be administered in just one daily dose, usually at bedtime. Since there is no correlation between the serum concentration of antipsychotics and their effect, the dosage is extremely individual; in fact, every patient should start with the smallest doses, then increase them until the effect is obtained. Then continue the therapy with such a determined dose.

Sometimes patients with schizophrenia do not cooperate in terms of taking medication regularly, so it is difficult to control the disease. In such situations, we can give patients an intramuscular injection of antipsychotics and that in the form of **a depot preparation** instead of the oral form. In the depot preparation, the antipsychotic is attached 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**). It gradually hydrolyzes the bond of the antipsychotic with the fatty acid or hydrolyzes the bonds in the microsphere polymer, and the antipsychotic is gradually released into the blood. It is enough to administer only one injection every 3 weeks, and for all that 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 around 70 kg)

ANTIPSYCHOTIC	INDICATION	METHOD OF APPLICATION	SINGLE DOSE	DOSE INTERVAL
Chlorpromazine	Delirium	intramuscular injection (i.m.)	50 mg	-
Chlorpromazine	Schizophrenia	orally	50 mg	8 o'clock
Thioridazine	Schizophrenia	orally	50-200 mg	8 o'clock
Fluphenazine decanoate	Schizophrenia	and . m .	25 mg	15 days
Risperidone	Schizophrenia	orally	1-8 mg	24 hours

ANTIDEPRESSANTS

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

Although the biochemical basis of major depressive disorder is still insufficiently clear, 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

opinion about 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"/ anti- depressants and selective serotonin reuptake blockers) or 2) by blocking the breakdown of mediators (inhibitors of the monoamine oxidase enzyme - MAO). All antidepressants show their effect ***only after a latent period of 2-4 weeks***, so during that period the patient should be intensively protected from suicide attempts.

Tricyclic antidepressants

Imipramine was the first drug from this group that was shown to be effective in suppressing the symptoms of depression (at the end of the 1950s). Later on, several more drugs of similar effectiveness and chemical composition (with three cycles in the molecule) were synthesized. All of them were called "tricyclic antidepressants" under the same name. 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, due to their chemical affinity with phenothiazines, are similar to the side effects of neuroleptics. They have an antimuscarinic effect (dry mouth, constipation, difficulty urinating, tachycardia, blurred vision) and in the cardiovascular system they can cause, in addition to tachycardia, postural hypotension (due to alpha 1 receptor blockade), while in predisposed persons they can cause an epileptic attack. Excessive sedation also poses a serious problem in therapy (caused by blockade of histamine H_1 receptors), especially when it comes to amitryptilin. H 1 receptor blockade 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 depressant effects), hypotensive drugs and MAO inhibitors (hypertensive crisis, hyperpyrexia, convulsions occur). Antipsychotics, oral contraceptives and some serotonin uptake blockers inhibit the metabolism of tricyclic antidepressants in the liver, thereby increasing the concentration of tricyclics in the serum.

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

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

Heterocyclic antidepressants

In an effort to overcome the mentioned side effects of tricyclic antidepressants, a large number of new compounds with a somewhat different mechanism of action - the so-called heterocyclic ("atypical") antidepressants or second-generation antidepressants (maprotiline, amoxapine, trazodone, nefa-zodone, mirtazapine, venlafaxine and bupropion) appeared. Amoxapine and maprotiline belong to heterocyclic antidepressants, but in effect and pharmacokinetics they are very similar to tricyclic antidepressants. Maprotiline has a particularly high tendency to cause convulsions, and amoxapine, among other things, also blocks dopamine receptors (it works like antipsychotics). Other heterocyclic antidepressants have significant specificities, such as fewer side effects than others (venlafaxine), a sedative effect (mirtazapine and trazdone) or causing insomnia (bupropion). In addition to the treatment of major depressive disorder, **venlafaxine is used with success 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 used today to treat depression, but as an aid for smoking cessation 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 some patients, trazodone causes liver cell damage, and in some men, priapism (prolonged and painful erection that sometimes ends in permanent neurological damage).

Selective serotonin reuptake blockers (SRBs)

Since 1987 a new group of the antidepressants has been introduced: selective serotonin reuptake blockers (fluoxetine, sertraline, paroxetine, citalopram, escitalo - pram and fluvoxamine). It has not yet been confirmed that serotonin uptake blockers are more effective than classic drugs, but they have worked successfully in some patients refractory to classic drugs.

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

Sometimes SBPS can cause "serotonin syndrome" due to excessive accumulation of serotonin (especially if given together with MAO inhibitors). This syndrome consists of hyperthermia, muscle rigidity, myoclonus, and confusion. In some patients, an increase in aggressiveness was observed after taking fluoxetine, and in a small number, an increased tendency to commit suicide. Paroxetine leads to an increase in the patient's body weight, and acts as a sedative, instead of an excitatory one.

Fluoxetine and paroxetine are strong, and sertraline is a weak **inhibitor** of the cytochrome P 450 2 D 6 isoenzyme. Therefore, they can interact with drugs that are metabolized by that isoenzyme and can increase their concentration in the blood, thereby increasing toxicity. Interactions with drugs that have a narrow therapeutic range are especially dangerous: with antiarrhythmics from group 1 C (encainide, flecainide, propafenone). Citalopram is distinguished from other SBPS by its extremely low potential for inhibiting the P 450 2 D 6 isoenzyme.

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

Monoamine oxidase 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 acts selectively only on dopamine. The first MAO inhibitors blocked the work of both types of enzymes (iproniazid, tranylcypromine, phenelzine, isocarboxazid). Later on, 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 administer than tricyclic antidepressants. The reason lies in numerous side effects, a smaller therapeutic range and interactions with the ingredients of some types of food. Side effects are somewhat similar to side effects 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. If they are overdosed, delirium, convulsions, hyperthermia and coma occur. During therapy with MAO inhibitors, the patient must not take aged cheese, smoked fish, wine and yeast. The mentioned 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 receptor and hypertensive crisis.

MAO inhibitors should not be given together with indirect sympathomimetics (ephedrine, amphetamine) and tricyclic antidepressants because a hypertensive crisis may occur. Therefore, their use together with opioids such as meperidine is contraindicated due to the occurrence of hyperpyrexia , hypotension and coma.

Due to 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 plant with significant medicinal properties. In medicine, the whole plant (herb) is used, usually dried and chopped; extracts for human use are usually made from the primary drug .

Most of St. John's wort's pharmacological effects are derived from hypericin, flavonoids and hyperforin. John's wort has an antidepressant effect; clinical studies have shown that its effect is similar to that of tricyclic antidepressants in major depressive disorder. However, it is still not clear when St. John's wort should be preferred over other antidepressants.

Choice of antidepressants

All antidepressants known so far have similar effectiveness, so the choice of drug is made according to the individual characteristics of the patient, side effects and response to the drug. In general, 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, one should try another, then a third, 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 " depressions (patients with tension, phobias and hypochondriasis) .

Antidepressants are usually administered for a few years, and then an attempt is made to discontinue them, if the patient is well. When stopping the use of antidepressants, it must be done GRADUALLY, i.e. gradually by gradually reducing the dose over 2-4 weeks. If the use of antidepressants is stopped suddenly, **withdrawal** syndrome occurs: nausea, lethargy, dizziness and headache.

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

Table 3. Doses of the most commonly used antidepressants (calculated per adult weighing around 70 kg)

ANTIDEPRESSIVE	INDICATION	METHOD OF APPLICATIO N	SINGLE DOSE	DOSE INTERVAL
Amitriptyline	Endogenous depression	orally	75 mg	24 hours
Imipramine	Nocturnal urination	orally	25 mg for children aged 6-7 years	24 hours
Trazodone	Endogenous depression	orally	150 mg	24 hours
Fluoxetine	Endogenous depression	orally	20 mg	24 hours
Moclobemide	Endogenous depression	orally	150 mg	12 o'clock

LITHIUM

Lithium is effective in the body in the form of the lithium ion (Li +), which is chemically similar to the sodium ion (Na +). The mechanism of action has not yet been fully clarified (for now, it is considered 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 70% of patients within 5-20 days) and in the prophylaxis of manic-depressive psychosis (ie 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. The elimination of lithium has a biphasic character. In the first 10 hours after taking the dose, the elimination is fast (40% of the dose is eliminated), and then it slows down. Therefore, it is recommended to take blood samples to measure lithium concentration only 12 hours after the last dose of the drug. The half-life of lithium is 12 to 24 hours.

Because of it's all tissues penetration, lithium has many side effects. It causes weight gain, disrupts the functioning of the thyroid gland (hypothyroidism), causes leukocytosis, antagonizes the effect of antidiuretic hormone in the kidney, leading to excessive excretion of dilute urine. It causes acne on the skin and can worsen psoriasis. Due to the effects on the CNS, hand tremors and sometimes confusion can occur. It works teratogenically!

Lithium is administered orally, in the form of lithium carbonate salt. The therapeutic range is very small (therapeutic plasma concentrations of lithium are from 0.5 to 1 mmol / l , and toxic ones 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 starting dose of lithium carbonate is 200 mg every 6 hours, orally. However, *it is necessary to control plasma concentrations of lithium during therapy and to adjust the dose according to them* - this is the only way to avoid toxic effects.

In order to prevent lithium intoxication, it is very important to maintain a normal sodium intake and to avoid the use of diuretics, which can lead to hyponatremia. If hyponatremia occurs, the toxicity of lithium increases, because it enters the cells more than usual.

Instead of lithium, the antiepileptics can be used to calm the symptoms of the acute mania and to prevent the manic and depressive episodes in the so-called bipolar disorder. These are: valproic acid, carbamazepine, lamotrigine or topiramate. Because of their simpler administration and slightly less 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 the prevention of manic and depressive episodes of bipolar disorder (an oral form of the drug is used for this indication).

EPILEPSY AND ANTI-EPILEPTIC MEDICINES

Epilepsy

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

All epilepsies can be classified into 2 groups: partial (also called "focal") and generalized.

Partial (focal) epilepsies can be simple (consciousness is preserved, involuntary movements or paresthesias occur only on one limb, sometimes there is activation of the autonomic nervous system) and complex (disorder of consciousness associated with stereotyped behavior, 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, partial seizures turn into generalized (secondarily generalized).

Generalized epilepsies can be distinguished only by a loss of consciousness (such an attack is called absence, from the English word *absence,* which means "absence", or *petit mal*, which in French means "small seizure") or the loss of consciousness is accompanied by contractions of the striated muscles (tonic-clonic seizures / tonic-clonic seizure is also called *grand mal*, French for

"big seizure"/, clonic seizures, tonic seizures or myoclonic seizures). There are also atonic attacks, which are characterized by a sudden loss of tone of the striated muscles.

Absence differs from all other epilepsies by the mechanism of its occurrence. It is caused by uncontrolled oscillations of electrical impulses between the thalamus and cerebral cortex. The electroencephalogram shows a characteristic picture: complex spike-wave, 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 origin and amplification of these oscillations.

Antiepileptics

The choice of antiepileptic drugs is based on the type of epilepsy, because most antiepileptic drugs only work on some forms of epilepsy. For the treatment of partial and tonic-clonic seizures, carbamazepine, oxcarbazepine, phenytoin, valproic acid, phenobarbital, lamotrigine, levetiracetam or topiramate are used. Apsans represents a specific form of epilepsy, which can only be treated with ethosuccimid or valproic acid. For atonic and myoclonic seizures, the drugs of choice are valproic acid, clonazepam or levetiracetam. In addition to the mentioned antiepileptics, there are drugs that are mainly used as additional therapy, in addition to the already existing "basic" antiepileptic: vigabatrin, gabapentin, topiramate.

The largest number of patients with epilepsy (90%) can be successfully treated with only one drug, while a small number 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 the seizures are controlled. If seizure control is achieved, the patient then remains on the same drug for a long time, with occasional control of the drug's serum concentration. If control is not achieved with the first drug, two more drugs should be tried individually; only in case of therapeutic failure with three individual drugs, the patient should be given a combination of antiepileptics. When changing antiepileptic drugs, the drug being replaced begins to be gradually withdrawn only after the full dose of the new drug has been reached.

A patient who has been prescribed an antiepileptic drug remains on such therapy for at least two years after the last attack. 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 can only drive private vehicles, provided that they have not had seizures for at least a year, or that they have not had seizures while awake for at least 3 years.

Carbamazepine and oxcarbazepine work primarily by blocking Na^+ channels in neuronal membranes. The blockade depends on the activity of the neuron: the more often the neuron generates action potentials, the greater number of its Na^+ - channels will be blocked by the drug (hence, antiepileptics have a certain selectivity of action, because they have the strongest effect on abnormally active neuronal groups; this property of antiepileptics is called "blockage dependent on use" - " use - dependent blockade "). Blockade of Na^+ - channels stabilizes the resting potential and reduces the excitability of neurons. In addition, these two drugs partially block the effect of the excitatory neurotransmitter glutamate on NMDA receptors.

Carbamazepine and oxcarbazepine have similar side effects, only they are less pronounced with oxcarbazepine. In addition to gastrointestinal complaints, diplopia, drowsiness, confusion, ataxia, generalized erythema, transient leukopenia and hyponatremia (due to potentiation of antidiuretic hormone) occur. Only carbamazepine induces the synthesis of the CIP 3A4 isoenzyme, thus accelerating the elimination of drugs that are metabolized by the same isoenzyme. This is especially important for other antiepileptics, oral contraceptives, warfarin and cyclosporine, whose blood concentration (and thus the effect) decreases significantly if they are used together with carbamazepine.

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

Phenytoin works on all forms of epilepsy, except for epilepsy. It blocks sodium and calcium channels, and potentiates the effects 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 pro - drug, is used for intramuscular administration, which is completely converted into phenytoin in the body. Elimination of phenytoin takes place through metabolism in the liver, and has **a saturation** character. Saturation of the metabolic pathway occurs already at therapeutic doses, so drug concentrations in the serum can vary greatly from patient to patient. This means that the dosing of phenytoin must be very careful, with the control of the concentration of the drug in the serum.

Unwanted effects of phenytoin are numerous, and significantly more frequent at higher doses. Tremor, nystagmus, blurred vision, ataxia, confusion, gastrointestinal complaints occur. The gums hypertrophy, facial features become coarser, acne appears, and in women, hirsutism. Like carbamazepine, it induces the metabolism of other drugs and vitamins. Due to the increase in decomposition, there is a lack of folic acid and vitamin D, so megaloblastic anemia and osteomalacia appear. It also accelerates the metabolism of warfarin and ciclosporin.

In addition to treating epilepsy, phenytoin is also used to treat neuropathic pain and arrhythmias.

Newer antiepileptic drugs that affect sodium ion channels are **zonisamide** (blocks sodium channels) and **lacosamide** (modulates sodium channels so that they accelerate their closing). They are used as additional therapy for partial epilepsies, which is facilitated by the fact that they interact poorly with other antiepileptic drugs. Zonisamide is more toxic, because it causes confusion, higher

frequency of renal calculus and oligohidrosis in children (difficult sweating). Lacosamide causes only vertigo 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 widest range of effects 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 effect of GABA, block T-type calcium channels and block the effect of glutamate on NMDA receptors. Due to 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 growth of curly hair, thrombocytopenia, tremors, ataxia and confusion. At the first time of therapy, valproic acid can cause severe chemical hepatitis (this is especially common in children under 3 years old). Therefore, liver function (transaminase level in the serum) must be monitored frequently during the administration of valproic acid. Valproic acid inhibits the metabolism of some antiepileptic drugs, increasing their concentration in the blood: 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 prophylaxis of migraine attacks.

Lamotrigine is a selective drug, blocking sodium ion channels only on neurons that use glutamate and aspartate as transmitters. Thanks to this effect, lamotrigine can prevent partial and generalized seizures.

Some of the side effects of lamotrigine are similar to side effects of carbamazepine: measles, drowsiness, diplopia, ataxia, headache, tremor. However, lamotrigine has one specific side effect: it causes *a flu-like syndrome*, most likely due to its influence on the synthesis of prostaglandins. In addition to the above, it is extremely important to know that lamotrigine must be introduced gradually into the therapy, i.e. from the minimum to the recommended maintenance dose, during 2 months. Otherwise, if you immediately start taking the recommended maintenance dose, Stevens-Johnson syndrome (appearance of bullae on visible mucous membranes and skin) may occur.

Phenobarbital and primidone are effective against all types of epilepsy, except against absence. 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 old people, the appearance of paradoxical excitement is possible, 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 (eg other antiepileptic drugs, cyclosporine, warfarin, oral contraceptives). It causes psychological and physical dependence.

Drugs that selectively block T-channels for calcium in the membrane of thalamic neurons are used to treat absences. These are **succinimides** (ethosuccimid) and oxazolidinediones (trimethadione). Ethosuximide has very few side effects (nausea and anorexia), so today it has completely replaced the more toxic trimethadione. In addition to absence, ethosuximide also has a beneficial effect on myoclonic, tonic and atonic seizures. The drug is well absorbed after oral administration, but it is slowly metabolized in the liver by cytochrome CIP 3A4 (half-elimination time 3 days).

Recently, drugs have been synthesized that can control resistant forms of epilepsy. **Gabapentin** is usually administered together with Na^+ channel blockers to control refractory partial epilepsies. Gabapentin increases the release of GABA from presynaptic terminals. In addition to the treatment of partial epilepsies, gabapentin is also used to treat pain in neuropathy.

Gabapentin may cause drowsiness, ataxia, fatigue, diplopia, tremor, and glycemic disturbances.

Vigabatrin increases the concentration of GABA by irreversibly blocking GABA-transaminase, the enzyme that breaks it down. And it is used only as an additional drug (along with the basic antiepileptic drug) in the treatment of epilepsy. Vigabatrin has a serious adverse effect on the retina: it leads to defects in the visual field. That is why its use today is limited only to those patients who do not respond to other antiepileptic therapy.

tiagabine has a very special mechanism of action . Tiagabine blocks the uptake ″of GABA into neurons and glial cells ″, thus increasing its concentration and effect, especially in the thalamus and hippocampus. In practice, it is used for the treatment of partial seizures, together with some other antiepileptic. Sometimes it causes tremors, loss of concentration and lethargy.

Topiramate, which works by blocking sodium channels, blocks AM PA receptors for glutamate and potentiates the effect of GABA, has proven to be the most effective of the new antiepileptics in clinical practice .

monotherapy of partial, then generalized tonic-clonic seizures, Lennox-Gestaut syndrome and West syndrome . The drug is relatively well tolerated; most of the side effects occur in the first 4 weeks: drowsiness, tiredness, difficult thinking process, confusion. After prolonged use, the appearance of kidney stones has 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 to prevent migraine attacks.

Two other antiepileptics work 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 due to potentially fatal side effects (aplastic anemia and fulminant hepatitis) is used only for partial epilepsies and Lennox-Gastaut syndrome that do not respond to other antiepileptic drugs. Perampanel can cause aggressiveness, anger, irritability and homicidal ideation.

Levetiracetam is used as monotherapy or in combination with other antiepileptic drugs for the treatment of partial epilepsies with and without secondary generalization, myoclonic seizures and tonic-clonic seizures. Levetiracetam binds to synaptic vesicles

and hinders the process of exocytosis. In patients, it causes emotional lability, insomnia, anxiety, aggressiveness and anorexia. A derivative of levetiracetam with the same mechanism of action is **brivaracetam** .

Just a few years ago ezogabine (another name is retigabine) entered clinical practice, which works by opening potassium channels, leading to hyperpolarization of the neuron membrane. It is effective in the treatment of partial epilepsies with and without secondary generalization. Ezogabine has two specific side effects: it causes urinary retention and bluish pigmentation of nails, skin, lips and retina.

All the mentioned antiepileptic drugs are actually used *in the prevention* of epileptic attacks. When an attack does occur, it usually lasts a short time and ends spontaneously. Sometimes, however, the attack can last over 30 minutes, so it is said that the patient enters **status epilepticus**. We must stop this state because uncontrolled muscle contractions cause serious metabolic disorders (lactic acidosis, hyperkalemia) that can endanger the patient's life. For discontinuation, benzodiazepines - diazepam or lorazepam - are used in the form of intravenous injection. 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 attack can be terminated by rectal administration of microenema with diazepam or administration of midazolam in the gingivo-buccal sulcus.

If the epileptic status does not stop even after 30 minutes of benzodiazepine administration, we can administer phenytoin, fosphenytoin or phenobarbital intravenously, with mandatory ECG monitoring. Fosphenytoin has an advantage over fentoin 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 even after 60 minutes from the administration of second-line drugs, there is no interruption of the epileptic status, the patient should be put under general anesthesia using intravenous anesthetics thiopentone sodium, midazolam or propofol.

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

ANTIEPILEPTIC	INDICATION	METHOD OF APPLICATION	SINGLE DOSE	DOSE INTERVAL
Carbamazepine	Grand Mall	orally	200 mg [1]	6 o'clock
Ethosuccimide	Petit mal	orally	250 mg for children under 6 years	24 hours
Phenobarbital	Partial epilepsy - shines	orally	150 mg	24 hours, in the evening
Phenytoin	Grand Mall	orally	100 mg	8 hours
Valproic acid	Myoclonic seizures	orally	5 mg /kg for children lighter than 20 kg [2]	6 o'clock

1. therapy starts with smaller doses (50 mg /6 hours), so they are gradually increased to the stated maintenance dose.
2. this dose can be gradually increased up to 10 mg / kg /6 hours, but only with control of transaminases and occasional measurement of drug concentration in the serum.

Interactions between antiepileptic drugs

Since antiepileptic drugs are sometimes combined, there is a possibility of interactions between them. Carbamazepine, phenobarbital and phenytoin are strong **inducers** of microsomal liver 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 (which leads to an increase in their concentration in the blood), and phenytoin displaces it from the connection with plasma proteins, leading to an increase in the concentration of the free fraction of the drug in the blood (and thus to an increase in the effect of phenytoin).

Antiepileptics in pregnancy

All antiepileptics have a teratogenic effect, but they must still be used during pregnancy, because an epileptic attack represents a very high risk for the mother and the child. Among them, lamotrigine is the least teratogenic, but it can also cause cleft lip and/or palate. Carbamazepine and valproic acid cause neural tube defects in 1 to 2% of pregnancies, which can be partially prevented by folic acid administration 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. That is why it is necessary to measure the concentration of antiepileptic drugs and adjust the dose according to the obtained results.

When the mother takes 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 (in the 36th week), as well as to the newborn.

Breastfeeding a child is possible with most antiepileptics, except for phenobarbital or some newer antiepileptics.

Antiepileptics in the treatment of bipolar disorder

Valproate and carbamazepine have shown efficacy in the treatment of ***mania***, which is of the same degree as the efficacy of lithium. Moreover, they also have a beneficial effect on patients who did not respond to lithium therapy. Both drugs are used both for suppressing an acute attack of mania and for maintenance therapy.

The mechanism of action of both drugs in mania remains unclear. They are thought to reduce the sensitivity of the brain 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 in a dose of about 1 g/day, orally.

In manic patients refractory to therapy with only lithium or valproate or carbamazepine, it is possible to use a combination of lithium with valproate or carbamazepine.

Valproate has also shown some effectiveness in preventing manic and depressive episodes in bipolar disorder type 1 (alternating fully expressed manic and depressive episodes), but far less than lithium. The use of antiepileptic drugs for the prevention of depressive episodes in bipolar disorder type 2 (alternating depressive episodes with hypomanic episodes) has been shown to be ineffective.

THERAPY OF PARKINSON'S DISEASE

The neurological disease manifested by 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 nigro-striatal dopaminergic pathway, because the neurons in the substantia nigra die. In these neurons, Lewy bodies first accumulate in the cytoplasm (made up of cytoskeletal proteins, alpha-synuclein, ubiquitin and synaptophysin) and the dark pigment neuromelanin, and then the cells die. Usually the cause of the damage is unknown, but sometimes it is not. For example, during the illegal manufacture of heroin, the drug is contaminated with 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MFTP), which in users of this drug destroys dopaminergic neurons and causes a severe clinical picture. parkinsonism (the so-called "frozen addict").

As already mentioned, Parkinson's disease is manifested by 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 (face it 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) Improvement of dopaminergic nigro-striatal activity times.

L-dopa. Dopamine alone cannot be used as a medicine because it has significant peripheral effects and poorly penetrates the CNS. That is why the dopamine precursor, 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 l-dopa administered orally is broken down in the intestinal wall under the action of dopa-decarboxylase. To prevent this, l-dopa is administered together with inhibitors of this enzyme: carbidopa or benserazide. L-dopa is easily converted to dopamine in the brain 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 unwanted effects of l-dopa are mainly the result of non-selective activation of other dopaminergic pathways in the brain. Since there are dopaminergic receptors in the vomiting center and the chemoreceptor zone associated with 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 can occur. Finally, an overdose of the drug produces dyskinesias: involuntary and purposeless movements. Sometimes the "on-off" phenomenon also occurs: the patient suddenly falls into complete immobility ("off"), only to spontaneously recover 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 administered together with sympathomimetics and non-selective MAO inhibitors, as a hypertensive crisis may occur. Also, the drug is contraindicated in patients with glaucoma with a narrow irido-corneal angle, because due to the mydriasis it causes, it can provoke a glaucoma attack.

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. That's why 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 therapy of early forms of Parkinsonism (usually given to younger patients whose intellect is preserved), or in advanced forms of the disease in which the nigro-striatal pathway has already completely degenerated, and the effect of L-dopa has weakened. Adverse 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, that is, to treat pituitary tumors that secrete prolactin or somatotropic hormone (because it suppresses the release of prolactin). While older drugs from this group (bromocriptine, pergolide and apomorphine) act on D_1 and D_2 dopamine receptors, newer drugs (prami-pexol and ropinirole) are selective D_2 receptor agonists. That's why newer drugs have fewer side effects (eg they don't cause retroperitoneal fibrosis).

In addition to the mentioned side effects, bromocriptine can cause spasm of peripheral arteries, and bromocriptine and pergolide can also cause retroperitoneal fibrosis. Due to its action on opioid receptors, apomorphine can also lead to respiratory depression.

While all other drugs from 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 the "off" period, that is, reduced mobility. It is rapidly metabolized in the liver, so its effect is short-lived. Rotigotine is applied as a transdermal patch.

Monoamine oxidase B (MAO-B) inhibitors. Dopamine is broken down in neurons under the action of the enzyme monoamine oxidase-B. Selective MAO-B inhibitors, **selegiline and rasagiline**, increase the level of dopamine in the brain, but do not affect the level of noradrenaline. Selegiline and rasagiline are used as monotherapy in the early phase of parkinsonism (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 parkinsonism (eg with L-dopa). They prolong the use of L-dopa and reduce the required doses of this 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 increase 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 the drug.

Amantadine. Amantadine increases the release of dopamine from nerve endings and prevents its reuptake. It has a weaker effect than other drugs, and tolerance to its effect occurs quickly. It is used mainly in patients who no longer respond to first-line drugs. Undesirable effects of amantadine are: confusion, insomnia, hallucinations, livedo reticularis (reticulated erythema on the skin) and orthostatic hypotension.

Entcapone is an inhibitor of the enzyme catechol-O-methyltransferase (KOMT), which breaks down a third of the amount of levodopa in the body. It does not cross 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 used together with L-dopa, and it slows down its breakdown. Side effects include hallucinations, dyskinesias and abdominal pain.

2) Decreased activity of the cholinergic striato-nigral pathway which normally has the opposite effect on motility than the nigro-striatal pathway.

Blockers of muscarinic receptors that penetrate the CNS can improve some symptoms of parkinsonism, primarily tremor, while they have a weak effect on bradykinesia and stiffness. Trihexyphenidyl, biperiden, benzatropine, and procyclidine are less effective than dopaminergic preparations, but may be useful when the effect of l-dopa wears off. They have classic antimuscarinic side effects: amnesia, dry mouth, constipation, difficulty urinating, paralysis of accommodation, difficulty sweating, etc. In addition, they cause confusion, hallucinations and impaired memory. 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 about 70 kg)

ANTI-PARKINSONIC	METHOD OF APPLICATION	SINGLE DOSE	DOSE INTERVAL
L-dopa with benzazide	Orally	100 mg + 25 mg	6 o'clock
Selegiline	Orally	10 mg , in the morning	24 hours
Bromocriptine	Orally	2.5 mg [1]	12 o'clock
Trihexyphenidyl	Orally	2 mg [1]	6 o'clock

1. therapy starts with smaller doses (1 mg/24 hours), so they are gradually increased to the specified maintenance dose.

Treatment of Parkinson's disease in younger people is usually started with selegiline or amantadine, and then switched to dopamine receptor agonists. In the elderly, L-dopa is the drug of first choice, because it less often causes confusion, which especially interferes with the daily functioning of the elderly. When after a few years L-dopa begins to lose its effect, amantadine, entcapone or selegiline can be added to it. Apomorphine can be administered parenterally in states of "disconnection" of the patient, and help him quickly (transfer 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 the secretion of saliva, they reduce the severity of that unpleasant problem.

TREATMENT OF ALZHEIMER'S DISEASE

Alzheimer's disease is a type of dementia, which is characterized by weakening of cognitive function (difficult thinking process) and memory loss. It affects about 10% of people over the age of 65. In the cortex of the brain (especially in the associative regions), hippocampus, amygdala and subcortical nuclei, beta-amyloid and Tau protein accumulate, and neurons fail. Amyloid is formed from a transmembrane pre-cursor protein that is torn into fragments by the enzymes beta and gamma-secretase; the most important fragment is the beta-amyloid protein, which makes oligomers, and then they connect and form amyloid. Tau protein normally stabilizes microtubules and allows the transport of neurotransmitter vesicles in neurons. In Alzheimer's dementia, the Tau protein becomes hyperphosphorylated and forms aggregates in the form of a network of fibers.

Reversible acetylcholinesterase inhibitors (tacrine, riva-stigmine, donepezil, galantamine) are still used in the treatment of Alzheimer's disease, but their effectiveness has been shown to be low. They can slow down cognitive decline in about 50% of patients, but for a few months at most. 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.

Nowadays, a blocker of NMDA receptors for glutamate called **memantine** is used with significantly greater success in the treatment of Alzheimer's dementia. Memantine is a derivative of amantadine. The most important side effects are constipation, hypertension and drowsiness.

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

Intensive research is underway for 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, because clinical studies have not shown favorable results.

In 2020, a drug against Alzheimer's disease with a completely new mechanism of action was approved for use in China. The drug has the code name **GV-971** , and it is an oligosaccharide from seaweed, which normalizes the disturbed bacterial flora in the large intestine. It was previously discovered that a disturbed intestinal flora activates some subsets of T-lymphocytes, which then penetrate into 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 various neurological disorders. Changes are visible in the brain's white matter on nuclear magnetic resonance imaging. The disease in the majority of patients has a course that is characterized by alternations of deterioration and improvement (relapse and remission). 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 the patient being bedridden and incontinent of urine and feces. A smaller number of patients from the beginning have the so-called primarily progressive form.

For a long time it was considered that T-lymphocytes are the main factors in the formation of inflammatory lesions in multiple sclerosis, but in the last few years, great progress has been made in understanding the role of B -lymphocytes . Drugs that reduce the number and activity of V-lymphocytes have been shown to be 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.

The primary therapy of 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 ideas in some patients, and in some it can lead to nephrotic syndrome or liver damage. Most patients get a flu-like syndrome after the injection. The effectiveness of interferon beta 1 is not great: it reduces the frequency of disease relapse from 3 in two years to 2 in two years, and it slows down the progression of the neurological deficit by twenty percent.

Now, instead of interferon beta 1 in the primary therapy of both relapsing-remitting and primarily progressive multiple sclerosis, the monoclonal antibody **ocrelizumab is used** , which binds to CD20 receptors on V-lymphocytes and leads to the destruction of lymphocytes that have this receptor on them. As a result, migration of V-lymphocytes into the central nervous system, presentation of antigens to T-lymphocytes, and inflammation with damage to nerve tissue are reduced. Ocrelizumab is far more effective than iterferon beta 1, and is administered intravenously only once every 6 months. The main side effect is an increase in the frequency of infections, especially viral ones (eg herpes).

In primary therapy **glatiramer** can also be used, a drug that resembles a protein from myelin. Glatiramer leads to the accumulation of T-helper type 2 lymphocytes 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, it reduces the frequency of relapse and somewhat slows down the progression of the neurological deficit. Redness and pain often occur at the injection site, and sometimes atrophy of the subcutaneous fatty tissue. Some patients after administration of glatiramer have a feeling of suffocation, their heart beats faster, and their face turns red.

Recently, drugs for multiple sclerosis that are administered orally have entered primary therapy: **teriflunomide** and **dimethyl fumarate**. Teriflunomide inhibits mitochondrial dihydroorotate dehydrogenase, which is necessary for pyrimidine synthesis, as a result of which the number of lymphocytes in the blood decreases. The clinical effect of teriflunomide is similar to that of interferon beta 1. Like other antimetabolites, it leads to bone marrow suppression, higher frequency of infections, thinning hair, diarrhea and sometimes liver damage. In addition, it raises 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.

Natalizumab, a monoclonal antibody against the integrin on the leukocyte membrane, is used as a secondary therapy, which prevents the adhesion of T-lymphocytes to endothelial cells and thus their arrival at the sites of demyelination in the central nervous system. It is administered as an intravenous infusion every 4 weeks. The effectiveness of natalizumab is greater than the effectiveness of interferon beta 1 (it reduces the frequency of relapse and the progression of neurological deficit more), but it has one serious side effect: it increases the risk of ***progressive multifocal leukoencephalopathy*** in people who are infected with ***the John Cunningham virus***. Therefore, the use of natalizumab is not recommended if this infection exists, and periodic checking of the presence of antibodies to the mentioned virus in the blood of patients receiving natalizumab is advised.

Fingolimod, a drug that binds to the receptor for sphingosine-1-phosphate, and leads to its internalization and degradation, is also used as a secondary therapy for multiple sclerosis. As a result, lymphocytes enter the central nervous system in a less extent. Fingolimod is administered orally. In terms of effectiveness, it is between interferon beta 1 and natalizumab. Among the side effects, it increases the frequency of respiratory infections and leads to bradycardia and A-V block.

Mitoxantrone (an antitumor antibiotic that interferes with the functioning of DNA, primarily in intensively dividing cells, and thereby reduces the number of lymphocytes that reach the central nervous system) and alemtuzimab (a monoclonal **antibody** against the CD 52 antigen on the lymphocyte membrane) are also used as a secondary therapy, which leads to the destruction of those cells and thus the reduction of inflammatory activity in the central nervous system. Mitoxantrone is administered once every three months, and alemtuzumab once a year. The effectiveness of these drugs is similar to that of natalizumab, but they have more side effects. Mitoxantrone has side effects typical of cytostatic drugs, and alemtuzimab increases the frequency of infections (prophylaxis against herpesvirus infections with aciclovir must be used), causes a flu-like syndrome after injection and can lead to various autoimmune diseases.

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

TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis is a degenerative disease based on the deterioration 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 it 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.

Recently, another drug has been approved that can slow the progression of amyotrophic lateral sclerosis: edaravone. **Edaravone** is an antioxidant administered intravenously, daily for 15 days of the month; for another 15 days, the patient is without therapy, until the beginning of the next month.

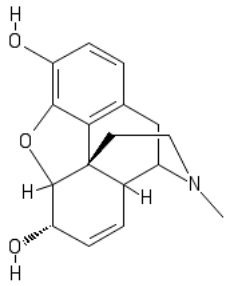
OPIOIDS

For centuries, opium, the juice obtained by cutting unripe poppy pods, has been used to relieve pain. Even in the "Odyssey" the use of an analgesic drink " ", probably opium, is mentioned. νεπενθεIn 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 of which are μ, κ, δand

nociceptin receptor (another name is "opioid receptor-like receptor"). Opioid receptors belong to the super-family of G-protein coupled receptors. Morphine binds particularly strongly to μ-receptors, which are the most widespread and have the greatest importance for pain control. There are three subtypes μof receptors: μ_1, the activation of which results in analgesic and euphoric effects, μ_2, the activation of which results in respiratory depression and bradycardia, and μ_3. κ-receptors (of which there are 4 subtypes) are predominantly located in the spinal cord; their activation achieves miosis, sedation, spinal analgesia and an increase in the release of antidiuretic hormone from the posterior lobe of the pituitary gland. δ-receptors (there are 2 subtypes) are found primarily in peripheral organs, and to a lesser extent in the central nervous system (modulate spinal analgesia). When -receptors are activated δ, in addition to the analgesic effect, there is also a neuroprotective effect. Opioid receptors that regulate pain are located on pathways that transmit information about pain (especially in the gelatinous substance of the posterior horns of the spinal cord and along the spino-thalamic pathway) and on structures in the cerebrum 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 importance of pain in the patient's consciousness.

The name "opioids" is used to denote all substances that bind to opioid receptors, and act similarly to morphine, an opium derivative. In addition to the endogenous opioids endorphins, enkephalins and dynorphins (discussed in the chapter on neurotransmission in the CNS), many exogenous substances, which we do not call exogenous opioids, can bind to opioid receptors.

Exogenous opioids are generally well absorbed from the digestive tract, and penetrate into all tissues, including the CNS. Opioids, especially morphine, should be used very carefully in pregnant women, because the liver of the fetus has a very small 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 analgetically (reduce the feeling of pain and the emotional reaction to it) and cause euphoria (a strong feeling of well-being). In people receiving morphine for the first time, instead of euphoria, dysphoria (effect on receptors) may occur. κThey reduce the frequency of breathing and the sensitivity of the respiratory center in the medulla oblongata to the concentration of carbon dioxide in the blood, which can lead to a complete cessation of breathing (*respiratory depression*). Opioids disinhibit the parasympathetic nucleus of the oculomotor nerve (3rd cranial nerve), as a result of which miosis occurs . By acting on the hypothalamus, these drugs increase the release of prolactin and antidiuretic hormone from the hypophysis. In the gastrointestinal and urinary tract, opioid agonists increase the tone of the sphincter and reduce the activity of the smooth muscles in the walls of the intestine or bladder, which results in constipation and retention of urine (in people who normally have difficulty urinating). Opioid agonists have an immunosuppressive effect (reduce cellular immunity), and can cause the release of histamine from mast cells (sometimes a feeling of itching occurs, and bronchoconstriction can occur in people with asthma). Finally, opioids suppress cough, i.e. they have an antitussive effect .

After long-term use of opioids with a high affinity for μ-receptors, people become **tolerant** to their effect (this means that it is necessary to increase the dose of the substance in order to maintain the effect) and the patient becomes **dependent**, which is *both psychological and physical* in nature. The brain structures "adapt" to the constant presence of the drug, so that when the drug is suddenly stopped, a disorder manifests itself in the following symptoms: dilated pupils, fever, sweating, nausea, vomiting, skin irritation, insomnia and a spike in blood pressure. We call the set of these symptoms one nam : abstinence syndrome. Withdrawal syndrome begins 6-12 hours after stopping the use of the drug, is strongest after two days and passes in less than a week.

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

If a person is addicted to opioids, they can get rid of their 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 canceling that other drug. This prevents the occurrence of a strong abstinence syndrome, because the organism 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 αare used : methadone or its derivative L -acetyl-methadol (LAAM), which has about twice as long half-life as methadone.

When opioid agonists are used to treat pain, they should be dosed continuously, at set intervals , so that the patient is not allowed to feel the full intensity of the pain again. It is a wrong practice to administer opioids "as needed", ie. when the patient asks (or rather moans) because he can no longer bear the pain; then the patient suffers, and the doctor has to administer higher doses than usual to relieve the pain.

Characteristics of certain exogenous opioids

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

Recently, the application of mor fin by the method of "patient-controlled analgesia" has been very popular. Morfin is administered parenterally, through an indwelling catheter, with the help of a computer-controlled pump . By pressing a button, the patient can inject himself with morphine, when he wants to, but only up to the maximum allowed by the computer program. This allows 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. Also, morphine should be avoided during childbirth, because it prolongs it and leads to respiratory depression in the newborn. During the use of morphine, the use of alcohol, sedatives, neuroleptics and other drugs with a sedative effect should be avoided, because the depressant effect on breathing is potentiated. Simultaneous administration of corticosteroids should also be avoided, due to potentiation of the immunosuppressive effect.

Codeine is also a natural alkaloid, found together with morphine in the pods of the opium poppy. It is far less effective 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. A part of ingested codeine is metabolized to morphine. Since codeine rarely causes euphoria, it is not abused.

Hydrocodone, oxycodone, dihydrocodeine, and oxymorphone are codeine or morphine derivatives used in combination with non-opioid analgesics to treat mild to moderate pain. **Oxycodone** is interesting for the fact that it does not expresses antitussive effect, so it can be used as an analgesic in lung patients, who must retain the ability to cough.

Meperidine (synonyms: pethidine, petantin) in addition to its analgesic effect also has a strong anticholinergic effect. Compared to morphine, it has a five times lower potency, which starts faster and lasts less (2 hours) than morphine. The metabolite of meperidine, normeperidine, has excitatory effects, causes mild agitation instead of sedation, and if overdose occurs, convulsions or hallucinations occur. It must not be given together with MAO inhibitors, because then convulsions are more common. Meperidine is often used for analgesia during childbirth because it has a shorter duration of action and is eliminated faster than morphine from the newborn's body; in addition, it strengthens the contractions of the uterus. Also, meperidine is useful as an analgesic in lung patients, because it suppresses cough less than morphine.

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

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

Fentanyl, sufentanil and alfentanil also have significant effects on the cardiovascular system, so they should be used with caution in people with diseases of that system. They cause bradycardia and hypotension due to vasodilation.

Levorphanol is the l-isomer of a morphine derivative, which has five times the potency of morphine. In all respects it resembles morphine, and in some countries it is used instead.

Methadone has a longer effect than morphine (~12 hours for methadone and ~4 hours for morphine) and accumulates in the body (in fat tissue). As a result, withdrawal from methadone is accompanied by a milder withdrawal syndrome than withdrawal from morphine. Today, methadone is mostly used to relieve withdrawal syndrome in morphine addicts. Also, it has been shown that in the case of a pregnant woman who takes heroin, it is useful to replace it with methadone, because the consequences for the future development of the child's cognition are less.

In the desire to overcome the bad sides - μagonists, synths - the so-called ***partial agonists***, i.e. drugs that bind to, but very weakly activate μ-receptors, and at the same time show great affinity for κ-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 stimulation of the heart) and cause excitation and hallucinations in the patient. This group of drugs includes pentazocine, butor - phanol, nalbuphine, buprenorphine and dezocine. If given together with morphine or some other strong β-μagonist, partial agonists block their action, and when given alone, they show strong κ- and weak μ- effects.

Pentazocine causes respiratory depression like morphine, but is much less likely to cause constipation. It is used to suppress pain of moderate intensity, and as a premedication of general anesthesia. Specific side effects of pentazocine are sedation, psychotomimetic effects (hallucinations, nightmares, anxiety) and heart 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 control moderate to severe pain. It has very similar side effects to pentazocine. It is administered parenterally or in the form of a nasal spray.

Tramadol is an opioid analgesic that also has the character of an antidepressant. Tramadol is a racemate, and both isomers, as well as the active metabolite, weakly activate mu-opioid receptors. One of the isomers blocks the reuptake of noradrenaline in the 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 confusion, which sometimes occurs. Tramadol has a weaker effect in about 15% of people, who have a genetically conditioned lower activity of cytochrome 2 D 6, so the active metabolite of tramadol is less formed. **Tapentadol** is a newer drug, which moderately activates the 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 confusion and is effective in all patients. Both drugs are administered orally.

There are also drugs that only block the action μof -agonists: naloxone, naltrexone and nalmefene. They bind to μ-recep - tors, but do not activate them. They are ***called opioid antagonists***. **Naloxone** is used to treat poisoning with morphine and other opioids. He can wake up a poisoned patient from a coma and establish spontaneous breathing. If used in patients who are dependent on μ-agonists, it can provoke the appearance of an abstinence syndrome. Naloxone is only given 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 administered multiple times to poisoned opioids.

Naltrexone is administered orally, and after absorption it is intensively metabolized in the liver. However, its main target, 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 the experience of euphoria. Naltrexone can help maintain abstinence in alcohol addiction. Unlike naloxone, which has almost no side effects, naltrexone has a hepatotoxic effect, causing headache, insomnia, increased blood pressure, increased appetite, blurred vision and delayed ejaculation.

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

Opioids used primarily as antitussives are dextromethorphan, noscapine, and levopropoxyphene. **Dextrome - Torphan** is the d-isomer of levorphanol. Levorphanol has no central effects, but only acts on the cough center in the medulla oblongata and depresses it. It must not be given together with MAO inhibitors, because it potentiates their side effects: hypertension and coma. Noscapine and levopropoxyphene have similar characteristics.

Table 6. Doses of the most used opioids (calculated per adult weighing around 70 kg)

OPIOID	METHOD OF APPLICATION	SINGLE DOSE	DOSE INTERVAL
Morphine	parenterally	10 mg	6 o'clock
Methadone	orally	5 mg	12 o'clock
Meperidine	intramuscularly	50 mg	6 o'clock
Butorphanol	intramuscularly	2 mg	4-6 hours
Naloxone	intravenously	0.4 mg	*

* It is given in case of poisoning with morphine or other μagonists . 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 applied again after 1-2 hours.

ADDICTIVE DRUGS

Medicines that affect the psychological functions of man have always been subject to abuse. In the desire to at least temporarily replace the often sad reality with illusions, people resorted to psychoactive substances. Unfortunately for them, repeated intake of these substances always leads to the user's addiction: the central nervous system adapts to the presence of a foreign substance (e.g. by reducing the number of receptors) so that a sudden cessation of intake causes a desire to use the substance again (psychic addiction). and in some cases unpleasant physical manifestations (physical dependence). A set of symptoms that occurs after stopping 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 pleasantness, well-being and sometimes excitement that resembles an orgasm), calming and relieving anxiety. Attention weakens, the thinking process is significantly more difficult and social considerations in behavior are lost. As the dose increases, loss of movement coordination, drowsiness and coma follow.

Among barbiturates with a short action pentobarbital, amobarbital and secobarbital are the most abused. The most commonly abused benzodiazepines are diazepam, lorazepam, flurazepam and midazolam.

Tolerance builds up over time to these substances, so it is necessary to take progressively higher doses in order to achieve the same effect. Both physical and psychological dependence develop, and the withdrawal syndrome is particularly severe (delirium, anxiety, sweating, hallucinations, muscle spasms, tremors and convulsions in about 2% of addicts). Abstinence syndrome is treated by repeated administration of substances from this group, and then by gradually reducing their dose. Benzodiazepines that are slowly metabolized (diazepam or chlordiazepoxide) are most often used, because their concentration in the blood gradually decreases upon cessation of administration, which gives the CNS time to adapt to the new environment. For example, diazepam is first given 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 for just one day before completely stopping the administration.

ETHANOL

Ethanol is a simple alcohol, with only two methyl and one hydroxyl group (SN_3SN_2ON). After oral administration, it is well absorbed from all segments of the gastrointestinal tract (up to 20% of the ingested amount is absorbed from the stomach); eating fatty foods before or during alcohol consumption slows absorption. After absorption, it is distributed both in the extracellular and intracellular spaces. 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 P 450 2E I**. Both enzymes transform ethanol into acetaldehyde, which is further transformed into acetic acid under the action of the enzyme aldehyde dehydrogenase from the cytoplasm.

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

Some drugs can inhibit the enzyme aldehyde dehydrogenase, and thus lead to the accumulation of acetaldehyde after the ingestion of ethanol. Acetaldehyde is a toxic substance that causes vasodilation, hypotension, facial flushing, headache, nausea and vomiting, chest pain, and difficulty breathing. One of the drugs with such an effect, ***disulfiram***, is used in the therapy of withdrawal of alcoholics, 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 includes increasing the activity of the receptor for the inhibitory neurotransmitter GABA, and decreasing the activity of the receptor for the excitatory neurotransmitter glutamate. Thus, ethanol actually has a depressing effect on the central nervous system. At the beginning of the effect of ethanol, due to the depression of the inhibitory functions of the brain, a person experiences euphoria, becomes aggressive and loses control over his behavior (the popular name of this stage is the "monkey stage"). Then there is difficulty in speech, ataxia, slowed down thinking process and slowing down of reflexes ("bear stage"), and eventually the person falls asleep and falls into a coma, with loss of control over the sphincters (popularly mocking "pig stage"). When the patient sobers up, ie. ethanol is metabolized, the patient develops **a hangover**, an unpleasant condition with headache, sweating, tremors and nausea.

Besides the central nervous system, ethanol affects other organs as well. It causes vasodilatation, especially in the skin, so that people intoxicated with ethanol cannot maintain body temperature, but instead 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. increases the excretion of diluted urine. In the stomach, ethanol increases acid secretion and leads to mucosal atrophy; in the small intestine, it damages the brush membrane of enterocytes and interferes with the absorption of amino acids and vitamins.

After chronic intake of large amounts of alcohol (in alcoholics), a whole series of organs are damaged. Cirrhosis develops on the liver, and myopathy on 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 (both in women and in men). Wernicke's encephalopathy (paralysis of the cranial nerves) and Korsakoff's psychosis (an alcoholic compensates for memory gaps with fabrications) develop on the brain.

If the mother takes alcohol during pregnancy (more than 90 ml per day), during the period of organogenesis, damage to the child occurs, which is 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, pointed nose with depressed nasal root, motor disorders, and anomalies of the heart, external genitalia and the inner ear.

In acute alcohol poisoning, the patient is usually in a coma when they reach the doctor. It is then essential to secure the airway and ventilate the patient if breathing stops. Administering glucose intravenously (obligatory with concomitant administration of vitamin B1) may be beneficial. In the most severe 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 action of glutamate. The consequence of this effect of acamprosate is a reduced desire to consume alcohol. Among the side effects, acamprosate can cause abdominal pain, itchy rash, decreased libido, and frigidity, i.e. impotence.

Opioid type of addiction. Of the opioids, the morphine derivative, heroin (diacetyl-morphine), is the most abused, which, due to its high liposolubility, reaches the brain the fastest, and thus acts the fastest. Heroin is most often administered intravenously, but it can be smoked or snorted. For a person who uses heroin for the first time, moodiness, nausea and vomiting usually occur. In long-term users, heroin and other opioids lead to euphoria and a sensation of heat passing through the extremities (similar to that of an orgasm). These feelings last for a few minutes, and then sedation and relaxation occur, lasting about an hour.

The use of opioids is accompanied by tolerance, psychological and physical dependence. Unfortunately, tolerance is weak for the depressant effect on breathing, and not at all for miosis and constipation. Withdrawal syndrome (dysphoria, anxiety, sweaty, and cold and clammy skin ["cold turkey"], rhinorrhea, vomiting, diarrhea, fever, muscle pain) is treated with the use of methadone, followed by its gradual discontinuation (20 mg daily 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, and 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 the salt to the base, they can also be ingested by smoking. Cocaine and methamphetamine can still be administered intravenously.

Both cocaine and amphetamine cause euphoria, an orgasm-like sensation, racing thoughts, excitement, anorexia, and increased alertness. These substances are most often used in periods of 1-3 days, when they are continuously taken in increasing doses; that's how it is - a given period is called a "run", and it ends with a "breakdown", i.e. physical exhaustion and sleep, which lasts 1-2 days. At higher doses, stereotypic movements (teeth grinding, continuous touching of the face, etc.) and paranoia occur. Outside the central nervous system, stimulants cause tachycardia, arrhythmias, hyperthermia, mydriasis, and increased blood pressure.

Their abuse is accompanied by psychological and weak physical dependence. Tolerance develops quickly, so during "races" doses are increased. Abstinence syndrome is mild (dysphoria, increased appetite, drowsiness) and does not require special treatment.

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 denote substances that disrupt perception, primarily visual and auditory. However, in addition to perception, hallucinogens also affect the thought process and mood. That is why, in addition to the term "hallucinogenic", the names "psychedelic" and "psychotomimetic" (imitate psychosis) are also used. This group of substances can be divided into two subgroups: ***phenylethylamine derivatives (*** mescaline, methylenedioxyamphetamine [MD ***A***] , methylenedioxymethamphetamine [MD MA] and dimethoxymethylamphetamine [DOM]) and ***indolamine derivatives*** (psilocybin, N , N -dimethyl - tryptamine [D MT], lysergic acid diethylamide [LSD]). Phencyclidine (PCP), an analog of piperidine, differs in its chemical structure from the mentioned groups, but also has a hallucinogenic effect. All hallucinogens have a high affinity for serotonin 5NT 2 $_{\text{receptors}}$, on which they act agonistically .

Natural alkaloids mescaline (from Mexican cactus without spines, peyote, Lophophora Williamsii) and psilocybin (from South American mushrooms, from which the preparation for ingestion, *ayahuasca,* was made) has been used by Indians for centuries to make contact with the spirits of ancestors, i.e. for plunging into one's own subconscious. Synthetic substances, primarily LSD, have been used by many artists as an aid to a better understanding of 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. A lot depends on the state the person was in before taking LSD, what the effects will be. A person who was relaxed, without fear, experiences euphoria, depersonalization, sees objects around him in a different way (from multiple viewing angles, with a clear texture, with stronger colors), loses the sense of time passing and sometimes has hallucinations of brightly colored geometric images. On the other hand, a person who was tense and scared can become even more anxious, experience a panic attack and get paranoid ideas.

M D MA is also known as "ecstasy". This substance has both a hallucinogenic and stimulating effect. In the beginning, euphoria appears, and the person who took ecstasy becomes more self - confident, and communicates with others more easily. Higher doses

cause hallucinations and stimulation of the cardiovascular system (tachycardia, hypertension, arrhythmias). MDA has similar effects , which in addition creates a feeling of closeness with others, so it is popularly called the "love substance".

Phencyclidine ("angel dust") has both a stimulating and hallucinogenic effect. A person under its influence feels happy, and believes that he works and thinks quickly and efficiently. Auditory hallucinations are especially common. In larger doses, it acts as an anesthetic (similar to ketamine), causing incoordination, catalepsy, amnesia, and then coma.

There is a marked tolerance to hallucinogens, which is crossed (eg if someone becomes tolerant to psilocybin, they are also tolerant to LSD and other hallucinogens). Addiction to hallucinogens is purely psychological in nature; abstinence syndrome does not exist.

Cannabis 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 resin from its buds), contains tetrahydrocannabinol, which causes euphoria accompanied by drowsiness, hallucinations, disturbed perception time, relaxation and weakening of immediate memory. The effects appear quickly, and will reach their maximum after 30 minutes, and last 4-6 hours. Tetrahydrocannabinol acts through its receptors, which are designated as CB 1, and which are found in high concentration in the cerebellum, extrapyramidal structures, hippocampus and cortex . In addition to the mentioned effects, tetrahydrocannabinol has an analgesic effect, increases appetite, causes tachycardia, pronounced hyperemia of the testicles ("bloodshot eyes"), bronchodilation and lowering of intraocular pressure.

There is only psychological dependence. Sometimes inexperienced people who enjoy marijuana or hashish experience a panic reaction and fear. No hangovers after using marijuana.

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

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

Nicotine addiction. Nicotine from cigarettes causes mild euphoria, increased alertness and reduces irritability. Both physical and psychological dependence develop on nicotine, which are extremely stubborn. Abstinence syndrome after quitting smoking, which consists of irritability, loss of concentration, increased appetite, and constipation, lasts for several months. With the use of small doses of nicotine released from special chewing gums, the abstinence syndrome can be overcome more easily.

Bu - propion, which acts as a selective inhibitor of noradrenaline and dopamine reuptake in nerve endings, can be useful in quitting nicotine. Bupropion must be dosed carefully, because in higher doses it can cause an epileptic seizure or acute psychosis.

Addiction to pregabalin. Pregabalin is a structural analog 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. It is used as a medicine 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 weaker movement coordination and tremors, so injuries are possible. An insatiable hunger appears, so the addict uncontrollably eats all the food he can get his hands on. Tolerance is created to the euphoric effect, so that the addict progressively takes larger and larger doses. When pregabalin is abruptly stopped, the withdrawal syndrome is relatively mild: headache, anxiety, sweating, diarrhea. A big problem in practice is the fact that the majority of doctors and pharmacists do not know the potential of pregabalin to cause addiction, so they prescribe and dispense it without sufficient control, thus encouraging the emergence of addiction.

NON-STEROID ANTI-INFLAMMATORY DRUGS

Apart from glucocorticoids, steroid hormones that, among other things, have anti-inflammatory effects, there are substances with a different chemical composition 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).

Inhibitors cyclooxygenase

Cyclooxygenase inhibitors prevent the formation of prostaglandin, thromboxane and prostacyclin. As all these substances are mediators in the inflammation process, the application of inhibitors leads to the calming down and withdrawal of all signs of inflammation. Cyclooxygenase inhibitors are used for the treatment of acute and chronic inflammations whose cause is not of an infectious nature (rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, bursitis and the like). Unfortunately, these drugs only work symptomatically; they have no influence on the progression of the disease itself. In addition to anti-inflammatory effects, all drugs from this group have analgesic and antipyretic effects. The antipyretic effect can be explained by blocking the production of prostaglandin E (Pg E) in the choroid plexus of the brain chambers under the influence of interleukin 1 from leukocytes; Pg E normally causes an increase in body temperature by setting the thermoregulatory center in the hypothalamus to a higher temperature.

Cyclooxygenase

The cyclooxygenase enzyme 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 an individual's life. COX 2 is primarily found in cells that participate in inflammatory processes (leukocytes, macrophages, etc.) and its activity increases significantly during inflammation. It is believed that by inhibiting COX 2 we achieve therapeutic effects in inflammation, while by inhibiting COX 1 we get unwanted effects. COX 1 is selectively inhibited by indomethacid, 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 under the popular trade name ***aspirin***. Aspirin is well absorbed from the digestive tract, and quickly after absorption is broken down under the action of 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 (major metabolic pathway) and oxidation to gentisic acid (secondary 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. With large doses of aspirin, the metabolic pathways in the liver become saturated; thus, the linear kinetics of elimination passes into saturation kinetics, and finally into zero-order kinetics. Thus, the half-elimination time of salicylic acid is 3-6 hours when applying small doses of acetyl-salicylic acid, and even 15-30 hours when applying large doses.

Acetylsalicylic acid irreversibly inhibits COX 1 and COX 2, while salicylic acid inhibits the same enzymes reversibly. Aspirin is used to treat mild and moderate pain, to lower elevated body temperature, as an anti - inflammatory agent in some rheumatic diseases and, in small doses, as an anti-aggregation agent.

If extremely large doses of aspirin are used (more than 4-5 g per day), the drug accumulates in the tissues and poisoning occurs. In the beginning, ringing in the ears and hyperventilation appear, 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 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 across chairs (due to blo kade synthesis prostaglandin E_1, which maintains until at least pro flow blood through the mucous membrane);
- small ones doses aspirin worsen gout , because make it difficult from secretion urinary acid in kidney . Big ones doses steam doxally increase excretion urinary wet lines ;
- deterioration functions kidneys (because are prostaglandins as needed For regulation flow blood in bark kidneys), followed by retention liquids ;
- the code small ones children aspirin can to challenge Ray's syndrome (ence fallopathy and insufficiency liver) if se near me in flow some viral infections (influenza , sheep smallpox). That's why is use aspirin the code children younger from 8 years old , i the code what's up children with viral infections , contraindicated ; _
- deterioration asthma (because se because of blockages synthesis pro staglan dina increases synthesis leukotriene , the main ones bronchocone strictor in asthma);
- if se these medicines applications the code a pregnant woman in the last one slow cutting pregnancy , I can put away the start childbirth and increase risk from the stillbirths ; children which se storks have got low weight on the birth and bigger risk from the intracra nial bleeding .

Salicylates (acetylsalicylic and salicylic acid) enter into serious interactions with other drugs, which have significant consequences. First of all, salicylates displace anticoagulants and sulfonylurea derivatives from plasma proteins; thereby increasing the free fraction of these drugs in the plasma, and lead to an increase in their effect, i.e. to bleeding, i.e. hypo-glycemia. Salicylates also increase the effect of insulin, and reduce the diuretic effect of the loop of Henle. Patients should be warned not to take alcohol together with aspirin, because the risk of developing acute stomach ulcers increases.

Apart from aspirin, this group of drugs includes acetic acid derivatives (indomethacid, diclofenac, ketorolac, tolmetin) , propionic acid derivatives (ibuprofen, flurbi - profen, ketoprofen, naproxen), oxicams (piroxicam), fena - mates (meclofenamate , mefenamic acid), pyrazolones (phenylbutazone and oxyfembutazone) and others (sulindac, ketorolac, etc.). In terms of effectiveness and side effects, these drugs differ to some extent from aspirin.

Acetic acid derivatives form a relatively heterogeneous group in terms of pharmacodynamics. **Indomethacin** is the most potent cyclooxygenase inhibitor, but due to severe toxicity (severe headache, gastrointestinal bleeding, bone marrow damage, coronary artery vasoconstriction, blurred vision, deposition in the cornea) it is only used when other drugs from this group are not effective: in severe rheumatic diseases and acute attack of gout. Also, it is used in prematurely born children, to cause closure of the ductus

arteriosus "Botali". Indomethacin is contraindicated in pregnancy, asthmatics and people with depression (because it can make it worse, by a currently unknown mechanism). From a functional point of view, *sulindac* and *etodolac* are very similar to indomethacide . Sulindac is a pro-drug, which is metabolized to an active sulfide metabolite; it damages the gastric mucosa less than indometacid, because when it is swallowed, as a pro-drug, it does not inhibit the synthesis of prostaglandins in the mucosa.

Diclofenac is not distinguished by any special characteristics, but **ketorolac is** remarkable for its strong analgesic effect (which may involve the release of endogenous opioids), which is why it is used for the treatment of postoperative pain.

Derivatives of propionic acid have a stronger effect than aspirin, with a lower frequency of side effects. This group of drugs includes ibuprofen, ketoprofen, fenoprofen, flurbiprofen and naproxen. The main difference between the drugs of this group lies in the duration of the effect: naproxen has a long half-elimination time, while ketoprofen, fenoprofen and ibuprofen have a short half - life.

Phenamates (meclofenamate and mefenamic acid) are effective cyclooxygenase blockers, but in children they cause more side effects than other cyclooxygenase inhibitors. Also, if these drugs are overdosed, they can provoke convulsions. That is why they are used only in patients who are resistant to the effects of other drugs from the group of non-steroidal anti-inflammatory drugs.

Pyrazolones (phenylbutazone and its active metabolite oxy-phenbutazone) are very effective anti-inflammatory drugs, but they often cause serious side effects (anemia, kidney failure, liver damage). That is why they are reserved only for the most severe pain, when other cyclooxygenase inhibitors have no effect. ***Oxicams*** (piroxicam) are characterized by their long-term retention in the human body, which allows one-day use.

In recent years, it has been seen that all non-steroidal anti-inflammatory drugs except aspirin increase the risk of myocardial infarction or brain infarction in patients with any cardiovascular disease, especially in those who have had a heart attack or have had an aorto-coronary bypass. The risk of myocardial or brain infarction increases with the dose and duration of use of these drugs. That is why a warning was added to the summary of the characteristics of all drugs from this group, and it was advised that they should be used as restrictively as possible in patients with cardiovascular diseases.

Table 7. Doses of the most commonly used inhibitors cyclooxygenases _

MEDICINE	INDICATION	SINGLE DOSE	DOSE INTERVAL
Acetylsalicylic acid	Analgesia	500 mg , orally	4-6 hours
	Anti-inflammatory effect	2 g , orally	8-12 h
	Antiaggregation effect	300 mg , orally	48-72 h
Ibuprofen	Anti-inflammatory effect	400 mg , orally	6 h
Piroxicam	Anti-inflammatory effect	20 mg , orally	24 h

Selective inhibitors of cyclooxygenase 2 are celecok-sib , rofecoxib and etoricoxib, drugs that are used only orally due to poor solubility. Since they inhibit constitutive cyclooxygenase 1 less than non-selective cyclooxygenase inhibitors, celecoxib and rofecoxib *cause gastric ulceration and bleeding less often* , so people with stomach diseases tolerate them more easily. In terms of effectiveness, they do not differ from non-selective cyclooxygenase inhibitors, except that they do not have an anti-aggregation effect.

Celecoxib , rofecoxib and etoricoxib have been widely used in recent years, which has also pointed out their downsides. It has been noticed that when using these drugs, ***the risk of hypertension and myocardial infarction increases several times***. 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 medicinal preparation with caffeine and/or smaller doses of opioid analgesics, primarily with codeine. It is believed that the effect of such combinations is somewhat greater than the effect of non-steroidal 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 the treatment of the patient difficult.

The others anti-inflammatory medicines

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. Those are:

1. Medicines against rheumatoid arthritis (gold , immunosuppressants , penicillamine , levamisole , antimalarials) _ _

2. Medicines For treatment gout (colchicine , allopurinol , febuxostat, probenecid and sulfinpyrazone)

1. Medicines against rheumatoid arthritis

Unlike all other anti-inflammatory drugs, members of this group slow down the progression of the pathological process and can delay the appearance of complications in rheumatic diseases. Their effect is not manifested immediately, but only after a latency of 1 month to one year. That is why 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 small doses, in which it is used to treat these diseases, methotrexate inhibits enzymes dependent on tetrahydro-folic acid, which normally break down adenosine. Therefore, adenosine accumulates inside and outside 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 marked toxicity (mucosal ulcers, hepatotoxicity, pneumonitis progressing to lung fibrosis, bone marrow depression, occurrence of infections), patients should be strictly monitored and timely measures taken to avoid or reduce toxic effects. Methotrexate is teratogenic, so it is not used during pregnancy and lactation.

Apart from methotrexate, other immunosuppressive drugs are also used: azathioprine (pro-drug, which is converted into mercaptopurine in the body) and ciclosporin.

Antimalarial drugs. Chloroquine and hydroxychloroquine (4-aminoquinolines) suppress the response of T-lymphocytes to mitogens, reduce chemotaxis of leukocytes 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 prolongation of the QT interval in the ECG. and photosensitisation. They can cause irreversible retinopathy after prolonged administration of higher doses (to prevent this, hydroxychloroquine is given in doses lower than 6.5 mg / kg and chloroquine in doses lower 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 pro-drug, which in the large intestine, under the influence of bacteria, is broken down into sulfapyridine and 5-aminosa-licylic acid, which has an anti-inflammatory effect. Sulfasalazine increases the concentration of adenosine, and prevents the release of tumor necrosis factor and interleukin 1.

Sulfasalazine causes gastrointestinal complaints (in 30% of patients), skin rash and dark discoloration of the skin, reduces male fertility and can increase the level of liver enzymes in the blood. It rarely causes bone marrow depression. It can provoke an attack of porphyria.

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 applied parenterally (aurothioglucose and gold-sodium-thiomalate) and orally (auranofin). Gold accumulates in synovial membranes, lymphatic vessels, spleen, liver and kidney. It weakens the functioning of macrophages and at that stage breaks 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 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 preparation causes diarrhea. Liver damage, peripheral nerve damage, gold deposition in the cornea and the so-called nitritoid reactions occur less frequently.

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

Penicillamine. Penicillamine is an analog 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 only used to treat 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 A_2, which prevents the synthesis of prostaglandins, leukotrienes and other mediators of inflammation. They do not slow down the progression of the pathological process, but act only 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 newer drug (it entered therapy only in 1998), which begins to work faster than other drugs that modify the course of the disease (in only 4 weeks). It is a pro-drug, which is produced in the body under the action of cytochrome R 450

oxidase converts it into an active form, which inhibits the proliferation of T-lymphocytes 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.

Diarrhea occurs in 30% of patients taking leflunomide, and 10% have nausea and vomiting. It causes skin rash with itching, alopecia, and elevated serum liver enzymes.

Leflunomide is teratogenic. It also inhibits cytochrome CIP 2 C 9, so it interacts with drugs metabolised by that enzyme (rifampicin and others).

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

Tofacitinib is a new drug that inhibits Janus kinases involved in joint inflammation. It is used to treat moderate to severe rheumatoid arthritis that has not responded to methotrexate therapy. Tofacitinib is administered orally, in two daily doses. Previous studies have shown that it can be used alone or in combination with methotrexate. The main side effects are more frequent infections.

Biological drugs for rheumatoid arthritis are proteins that are obtained from living cells, ie. cytokines or their blockers. They are used to treat moderate to severe rheumatoid arthritis that no longer responds to the above medications. They are used alone or in combination with methotrexate. **Etarnecept, infliximab, adalimumab, golimumab and certolizumab** block tumor necrosis factor, **tocilizumab** blocks interleukin 6, **abatacept** prevents T-lymphocyte activation, **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 biologics are administered subcutaneously. Medicines that block the tumor necrosis factor can lead to bacterial, fungal and viral infections, as well as malignant tumors (lymphoma, skin cancer, etc.). Rituximab leads to progressive multifocal leukoencephalopathy and heart rhythm disorders in a certain number of patients. Abatacept worsens chronic obstructive pulmonary disease.

Diet. Patients should be advised to take plenty of marine fish that contain large amounts of eicosipentaenoic acid (fatty acid of 20 C atoms with 5 double bonds). This acid is incorporated into human cell membranes and gradually replaces arachidonic acid, which is the precursor of many inflammatory mediators.

Table 8. Doses of some drugs against rheumatoid arthritis

MEDICINE	METHOD OF APPLICATION	DOSE
Auranofin	Orally	6 mg /24 h
Hydroxychloroquine	Orally	200 mg /24 h

2. Medicines for the treatment of gout

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

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 done 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 cells. Whether uric acid will be net excreted or reabsorbed depends on the balance of the reabsorption and secretion systems. Reabsorption of uric acid is blocked by probenecid, sulfinpyrazone and salicylates, while secretion is hindered 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, and causes inflammation. Granulocytes phagocytose uric acid crystals and then release lysosomal enzymes and lipids, which attract other granulocytes. Apart from 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 (with the exception of acetylsalicylic acid, which inhibits uric acid excretion), 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. Medications to prevent attacks should never be given during an acute attack of gout, because they initially increase the concentration of uric acid and can worsen the patient's condition.

Colchicine is an alkaloid, which has been used for the treatment of gout in extracts of various plants since the 6th century AD. It binds to microtubules of leukocytes, leads to their depolymerization and thus hinders their movement towards the site of inflammation.

Therapy with colchicine is started at the appearance of the first signs of an attack, and 1 milligram is given, then about an hour later another half 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 larger doses, which, due to excretion through the bile, primarily causes gastrointestinal complaints: nausea, vomiting, abdominal pain and severe diarrhea in most patients (80%). It rarely leads to alopecia, bone marrow depression and neuritis.

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

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

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

Sulfinpyrazone is chemically similar to phenylbutazone, but has no anti-inflammatory properties. Adverse effects of sulfinpyrazone are manifested in the gastrointestinal tract: nausea, activation of stomach or duodenal ulcers, abdominal pain.

Benzbromarone is the most effective of all drugs in terms of lowering blood uric acid (including allopurinol and febuxostat), which is due to its active metabolite formed in the liver. However, benzbromarone is not available everywhere, 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*** (a hypoxanthine analogue) and ***febuxostat*** competitively inhibit the enzyme xanthine oxidase and thereby prevent the formation of uric acid. The body accumulates hypoxanthine and xanthine, which are much more soluble than uric acid, so they are easily excreted from the body.

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

Since the administration of allopurinol at the beginning can 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 alkalinize the urine). Sometimes colchicine can 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 through the kidneys and through the bile.

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

PARACETAMOL

Paracetamol (synonym: acetaminophen) is an analgesic-antipyretic. It originates from phenacetin, which was withdrawn from use due to high nephrotoxicity. Acetaminophen has analgesic and antipyretic effects, but does not have significant anti-inflammatory and anti-aggregation effects. Unlike cyclooxygenase inhibitors, it has no irritating effect on the gastrointestinal tract. It is the antipyretic of choice (dose is 500 mg /4-6 hours orally). Its use during 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 non-steroidal anti-inflammatory drugs lies in the fact that it does not increase the risk of gastric stress ulcers.

In smaller doses, paracetamol is well tolerated, but higher doses (greater than 4 grams per day) can lead to the accumulation of the highly toxic secondary metabolite N-acetyl-p-benzoquinone, which causes centrolobular necrosis of the liver. When the liver runs out of glutathione, which binds to the toxic metabolite and neutralizes it, the mentioned centrolobular necrosis occurs. From the moment of oral administration of a toxic dose of paracetamol, a latent period of 12-24 hours should pass before the first symptoms of poisoning (nausea, vomiting) appear, and even 72 hours before the appearance of signs of liver damage. Acetaminophen poisoning is treated with a donor of sulfhydryl groups, acetylcysteine, which instead of glutathione binds to benzoquinone and prevents its toxic action. Acetylcysteine is administered orally.

NEFOPAM

Nefopam is a non-opioid analgesic with central action, which prevents 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 equivalent analgesic effect to 6-12 milligrams of morphine administered intravenously.

Nefopam is used when non-steroidal anti-inflammatory drugs cannot control the pain, and it is not yet necessary to use opioid analgesics.

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: TNF αor cachectin, which is produced by macrophages, and TNF βor lymphotoxin, which is produced by lymphocytes.

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

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

Locally, TNF αcauses 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 does not respond to other drugs that modify the course of the disease. It is administered as a subcutaneous injection, 40 mg twice a month, usually together with other drugs for rheumatoid arthritis.

Adverse effects of adalimumab are: redness, pain and swelling at the injection site; increased frequency of serious infections and sepsis; rarely the appearance of lymphoma or demyelination.

Infliximab is a chimeric monoclonal antibody to TNF α, created by joining 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 body weight, at intervals of 2, 6 and then 8 weeks.

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

Both adalimumab and infliximab are effective only in some patients, so if positive effects are not seen after three months, further use should be discontinued.

Etarnecept is a soluble receptor for TNF (p 75). When administered, it binds to TNF and prevents its interaction with endogenous receptors. It has shown effectiveness 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 about 115 hours.

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

Golimumab is a monoclonal antibody that binds to TNF alpha, both the form that is already in circulation, and 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 from this group, it reduces the patient's resistance to infections.

Certolizumab is a soluble Fab fragment of a humanized antibody that binds to TNF alpha, both in the form that is already in circulation and in the form that is bound to cell membranes. Both its effectiveness and side effects are similar to other drugs from this group.

INTERLEUKIN 1 and 6 ANTAGONISTS

Interleukin 1 (IL 1) and interleukin 6 are important mediators of inflammation and joint damage in patients with rheumatoid arthritis. Recently, an interleukin receptor blocker, the protein preparation ***anakinra, has been used in clinical practice.*** By binding to receptors for IL 1, anakinra blocks the action of endogenous IL 1 and thereby improves the clinical picture in patients with rheumatoid arthritis. Its effect is somewhat weaker than that of TNF antagonists. Anakinra is administered subcutaneously. A

monoclonal antibody against the receptor for interleukin 6 (***tocilizumab***), which is administered as an intravenous infusion, also slows down the course of rheumatoid arthritis and improves the clinical picture.

The biggest problem with the use of anakinra and tocilizumab is the increased frequency of serious infections in patients receiving them. In addition, the number of neutrophils and thrombocytes decreases.

NEUROMUSCULAR BLOCKERS

Motor nerves release the transmitter acetylcholine at their endings. Acetylcholine binds to nicotinic N_2 receptors on the membrane of striated muscle cells (N_1 nicotinic receptors are located on the membranes of ganglion cells and sympathetic and parasympathetic cells) 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 that 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 nicotine receptors, prevent the action of acetylcholine and thus temporarily paralyze the striated muscles. There are two types of blockers. ***Succinyl-choline*** first activates nicotinic receptors and leads to membrane depolarization (small fasciculations can be seen on the patient), and then the membrane is kept 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, a partial repolarization of the muscle cells occurs, so that there is a so-called "double-type blockade": a part of the muscle cells is depolarized, so such a blockade cannot be suppressed by the use of acetylcholinesterase blockers, while a part of the muscle cells is repolarized, so such blockade can be suppressed by the use of acetylcholine-esterase blockers.

Another type of neuromuscular blockers consists of substances that bind to nicotine receptors, but do not activate them. They are ***non-depolarizing blockers***, which are divided into two sub-groups: (1) isoquinoline derivatives (mivacurium, atracurium, cisatracurium, doxacurium and tubocurarine) and (2) steroid derivatives (pancuronium, vecuronium, rocuronium, pipecuronium). These drugs also lead to muscle paralysis.

Neuromuscular blockers first lead to paralysis of 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 proceeds in the reverse order of the one in which the paralysis occurred.

All neuromuscular blockers have a similar chemical structure to acetylcholine, which means they have **quaternary nitrogen** in their molecule. Due to the electric charge of quaternary nitrogen, neuromuscular blockers cannot pass through body membranes by simple diffusion, so they are not absorbed from the gastrointestinal tract, do not penetrate through the hemato-encephalic 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, succinylcholine (after half to one minute) and rocuronium (after 2 minutes) have the fastest onset of action, while other neuromuscular blockers take 3 to 5 minutes to take effect. The effect of succinyl-choline lasts the shortest, only 5-10 minutes, because it is quickly broken down by pseudo-cholinesterase from the blood. The duration of action of non-depolarizing neuromuscular blockers ranges from 20-30 minutes (rocuronium, mivacurium, atracurium, cisatracurium) to 60-90 minutes (pancuronium, pipecuronium, doxacurium); their action ends due to redistribution, as a result of which the concentration in the vicinity of nicotine receptors decreases. Only later do they break down spontaneously (atracurium and cisatracurium), they are broken down by pseudocholinesterase in the blood (mivacurium), they are metabolized in the liver (vecuronium) or they are mostly excreted unchanged in the urine (rocuronium, pancuronium, doxa-curium, pipecuronium). This means that in the event of an overdose, the duration of the neuromuscular blockade is extended several times.

In one person out of about 3000, there is a hereditary lack of -pseudocholinesterase in the blood, so that they cannot break down succinylcholine and mivacurium, if administered to them. In them, the neuromuscular paralysis caused by succinylcholine or miva curium lasts for 2-3 hours, until these drugs are excreted through the urine.

Succinyl-choline is given to patients during induction of general inhalation anesthesia in order to facilitate endotracheal intubation. Rocuronium can also be used for the same indication, due to the rapid onset of action. Other non-depolarizing blockers are added during general inhalation anesthesia to ensure sufficient muscle relaxation, necessary for abdominal and thoracic surgery. In addition, with their help, electric shocks are administered in psychiatric institutions: then there are no muscle spasms that were once accompanied by even bone fractures! Sometimes it is necessary to apply non-depolarizing neuromuscular blockers to stop convulsions in status epilepticus or tetanus, or in situations where the patient is artificially ventilated.

The effect of non-depolarizing blockers lasts about 1 hour. If it is necessary to stop their action earlier, the acetylcholinesterase inhibitor neostigmine is used. Neostigmine leads to an accumulation of acetylcholine, which displaces the blockers from the receptors and terminates the muscle paralysis.

The action of rocuronium and vecuronium can also be stopped with a drug called ***sugammadex***. This drug binds directly to rocuronium or vecuronium and thereby interrupts their effect on nicotinic receptors.

The side effects of non-depolarizing neuromuscular blockers are not very pronounced, and are mainly due to the blockade of muscarinic receptors in the heart (tachycardia occurs with pancuronium, rocuronium, atracurium and mivacurium) and the release of histamine from mast cells (redness of the face, 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 (increase in body temperature, muscle stiffness, tachycardia and acidosis).

THERAPY OF MUSCLE SPASMS AND SPASTICS

A muscle spasm is a sudden contraction of one or more muscles (which may last shorter or longer), while **spasticity is** a continuous contraction of a number of muscles. As part of many neurological diseases, spasticity of the striated musculature occurs, which makes it very difficult for patients to move and work. The basis of spasticity is damage to the central motor neuron (for example, in children's cerebral palsy, after a stroke, in multiple sclerosis) as a result of which control over spinal reflexes and reflexes involving cranial nerves is lost. Reflexes become hyperactive, resulting in spasticity.

Since central neuron damage cannot be treated at the moment, it is only possible to reduce reflex hyperactivity. This can be done by increasing inhibition in the CNS, ie. facilitating the action of inhibitory transmitters. There are drugs that act only on muscle spasms (such as **cyclobenzaprine** , which is not approved for use in Serbia), and those that are active on both muscle spasms and spasticity (benzodiazepines, baclofen, tizanidine, gabapentin). Medicines with a peripheral effect, dantrolene and botulinum toxin, also work on spasms and spasticity.

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. Adverse effects of baclofen are confusion, hallucinations and ataxia. If its use is stopped suddenly, 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 metabolized already during the first passage 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 thought to somehow inhibit calcium ion channels and thus lead to relaxation of muscle contraction. Otherwise, it is a drug that is characterized by complete elimination through the kidneys and a weak potential for interactions with other drugs. Side effects are drowsiness, nausea and fatigue.

In severe forms of spasticity, medication can also be used with the peripheral effect **of dantrolene **, which prevents the release of calcium ions from the sarcoplasmic reticulum by blocking the ryanodine calcium channels on that organelle. Effectively suppresses spasticity, but therefore can cause muscle weakness. It can rarely 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 (eg 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 cholinergic nerve endings (including motor nerves), and prevents the release of acetylcholine there. The effect of the injection occurs after 3 days and reaches its maximum after 2 weeks; lasts up to 12 weeks, after which the injection should be repeated. After the injection, a transient burning sensation occurs; the appearance of antibodies to botulinum toxin is possible. Recently, botulinum toxin has started to be successfully used for spasms ***of several muscle groups***, e.g. on the upper or lower extremity after a stroke, or with spasms that follow a child's cerebral palsy.

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

Table 9. Doses of antispasmodics

MEDICINE	INDICATION FOR APPLICATION	DOSE
Baclofen	Spasticity of spinal origin	10 mg /day orally initially, later up to 20 mg /8 hours.
Diazepam	Spasticity	4 mg /8 hours orally
Dantrolene	Spasticity	25 mg /12 hours initially, later up to 50 mg /6 hours

ESSENTIAL TREMOR

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

Primidone, a drug that is metabolized in the body into phenobar-bitone, can also be used in the therapy of essential tremor . The drug is effective, but side effects are particularly common in these patients (sedation and ataxia).

If essential tremor does not respond favorably to pro-pranolol or primidone (30-50% of patients), it can be treated with antiepileptics **gabapentin** or **topiramate**, beta blockers atenolol or sotalol, or 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 from the cytoplasmic side and thus prevent the occurrence of an action potential, i.e. interrupt the spread of information along the nerves. Local anesthetics first block unmyelinated and poorly myelinated nerve fibers (S and A δ), and only later thick, fully myelinated fibers (A $\beta$and A αfibers). That is why, after the application of local anesthetics, the sensation of pain and heat is primarily lost, while the sensation of touch and the function of the motor nerves are mostly 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 primarily depends 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 (eg adrenaline) to the local anesthetic, the action can be significantly prolonged. The effect of esters is shorter (about 45 minutes) and because they are broken down by pseudocholinesterase from the blood plasma, and the effect 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 dripped 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). Insensitivity is achieved about 10 minutes after the injection (that's why you should always wait 10 minutes after applying the anesthetic before starting the intervention!) and lasts about 1 hour. During that time, it is possible to perform a minor surgical intervention.

For surface anesthesia, benzocaine (in the form of drops, for anesthesia of the mucous membrane 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 mucous membrane of the oral cavity) .

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, tremors, even convulsions) and the cardiovascular system (tachycardia, hypotension, arrhythmias). While esters can cause allergic reactions, this happens extremely rarely with amides. Most often, patients become allergic to para-amino benzoic 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.

Special toxicity among local anesthetics is shown by **bupivacaine** which binds with great affinity to the conduction system of the heart and causes serious ventricular arrhythmias. That is why less toxic drugs, such as its optical isomer levobu-pivacaine or its chemical analogue ropivacaine, are increasingly being used instead of bupivacaine. **Ropivacaine** it acts less toxic on the central nervous system and myocardium, and shows less tendency to cause motor nerve block.

Articaine is a newer local anesthetic that differs from other amide anesthetics in that it also has an ester group that is broken down by plasma esterases. That is why it is quickly metabolized after entering the systemic circulation, so it exhibits less toxic effects on the central nervous system and the heart. Today, it is widely used for local anesthesia in dentistry, then in people with liver or kidney failure, in the elderly and in children.

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

Tetrodotoxin and saxitoxin

Two very strong natural poisons, tetrodotoxin and saxitoxin, work by a mechanism similar to that of local anesthetics. They also block Na^+ channels, but do so on the outside of the membrane. Tetrodotoxin is found in the liver and ovaries of the Japanese "balloon fish" (in case of danger, this fish inflates like a balloon); saxitoxin is created by micro-organisms that make up plankton, and accumulates in shellfish tissues. Both poisons cause paralysis.

GENERAL ANESTHESIA

General anesthesia is a state of depression of the CNS characterized by loss of consciousness and cessation of central processing of sensory information from the periphery (no response to pain, tendon reflexes cannot be evoked). It can be achieved with inhaled or intravenous anesthetics. Anesthesia has several stages that the patient goes through, depending on the anesthetic dose. The first phase (phase of analgesia) occurs at the beginning, while anesthetic concentrations in the blood are still low. The patient is fully conscious, but the feeling of pain has been lost. With the further application of anesthetics, the second phase occurs - the phase of delirium. Then the patient is restless, with tense muscles, confused, able to get up from the operating table. In modern general anesthesia, rapid administration of drugs practically eliminates this phase. The third phase of anesthesia is called surgical, because surgical interventions are performed in it. It is divided into 4 subphases that differ from each other 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 stage there is a depression of breathing and the work of the heart, which results in a fatal outcome.

When we put a patient under general anesthesia for some kind of surgical intervention, we want to achieve the following: (1) rapid loss of consciousness; (2) sufficient depth of anesthesia to prevent reflex reactions to pain (eg, reflex bradycardia during manipulation of the patient's intestines on the operating table); (3) minimal and reversible impact on vital physiological functions (breathing and heart rate); (4) skeletal muscle relaxation; (5) rapid recovery from anesthesia, and (6) safety in anesthetic administration (no risk of explosion or fire). Since none of the currently known anesthetics can meet all the mentioned requirements, a combination of several anesthetics and other drugs is usually used; we call such general anesthesia ***balanced anesthesia***.

general inhalation anesthesia

Some gases (nitrogen suboxide, N_2O) and vapors of easily volatile liquids (ether, halothane, enflurane, isoflurane, sevoflurane, de-sflurane) which reach the bloodstream through inhalation and the alveolo-capillary membrane, and then into the CNS, 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 (eg halothane) are partially metabolized in the liver.

How fast the anesthesia will start after drug administration and how fast the patient will wake up after stopping the drug administration depends primarily on the solubility of the anesthetic in the blood and fat tissue. Anesthetics that are poorly soluble in blood and fat tissue (nitrogen-suboxide) quickly begin to work and quickly stop working, because they easily lead to the saturation of these media. On the other hand, anesthetics that are highly soluble in blood and fat tissue (e.g. halothane) begin to work slowly, their effects end slowly (because a large amount of the drug has dissolved, so it takes more time for elimination) and cause a long-lasting "hangover" after the end of anesthesia (because they are very slowly withdrawn from the fatty tissue in which they 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 applies anesthetic gas or steam by changing their partial pressure in the air that is injected into the patient's lungs using a respirator on the anesthesia machine. At the beginning of anesthesia, the partial pressure increases, so that the gas or vapor passes into the blood (and from them into the tissues); when anesthesia needs to be stopped, the supply of anesthetic gas or vapor is interrupted, so they pass from the tissue 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 with movement to a skin incision, is called ***the minimum alveolar concentration (MAC)***. It is usually not expressed in pressure units, but as a percentage of all the gases in the mixture that the anesthesiologist uses a machine to inject into the patient's lungs. MAK is an indicator of the strength of the anesthetic effect. For example, the MAK of sevoflurane is 2%, and the MAK of nitrous oxide is more than 100%. This means that we can achieve anesthesia with only 3-4% sevo-flurane in the inhaled air, while we cannot do it with 100% nitrous oxide (that's why nitrous oxide is never used alone, but in combination with other anesthetics) .

Nitrogen suboxide is therefore not a strong enough anesthetic, so it cannot provide the required depth of anesthesia by itself; 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 (a combination of fentanyl and droperidol, known under the name Talamonal ^{R}, is especially frequently used). General anesthesia in which additional neuroleptics are used is called "neuroleptic-anesthesia".

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

Nitrous oxide is popularly called "laughing gas", because at the beginning of application, at lower concentrations, it leads to disinhibition and uncontrollable giggling of the person who inhales it. By applying gas more quickly, this phenomenon can be avoided.

Halothane, desflurane, sevoflurane, isoflurane and enflurane are halogenated hydrocarbons, which evaporate easily at room temperature. ***Halothane*** depresses the respiratory center and the cardiovascular system (direct depression of the myocardium, inhibition of the baroreceptor reflex, hypotension), desensitizes the myocardium to catecholamines and reduces blood flow through

the coronary arteries. It also reduces blood flow through the kidneys (thereby reducing diuresis), and increases blood flow through the brain and intracranial pressure. It is an extremely strong anesthetic (MAK=0.5%), but should be used with caution in people with heart, kidney or CNS injuries.

Halothane is oxidized in the liver, producing 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 never used today because it is explosive, because it irritates the airways and causes a pronounced delirious phase of anesthesia. Nevertheless, 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 of the world have it in their war reserves.

enflurane depresses the cardiovascular system (direct depression of the myocardium, hypotension, but without blocking the baroreceptor reflex) and sensitizes the myocardium to catecholamines. It can sometimes cause tonic-clonic seizures in anesthetized patients. Since during its metabolism, the fluoride ion is released, which has a toxic effect on the kidney tubules, sometimes a temporary impairment of kidney function may occur.

Isoflurane is effective and a slightly toxic inhalation anesthetic: it does not depress the cardiovascular system, widen the coronary arteries and does not sensitize the myocardium to catecholamines. Also, during its metabolism, far fewer fluoride ions are released than with enflurane. The downside is isoflurane, which causes transient, mild tachycardia, due to direct sympathetic stimulation; should be careful in people with coronary disease. It also causes respiratory tract irritation, but less so than desflurane.

Sevoflurane is less soluble in blood than other anesthetics from this group, so its effect starts faster. It is more popular than other inhalation anesthetics because it does not cause irritation of the respiratory tract. It leads to vasodilatation and a decrease in cardiac output, increases blood flow through the brain and raises intracranial pressure. There is a suspicion that in contact with absorbents for carbon dioxide, which are found in anesthesia machines, substances with a nephrotoxic effect are formed. Sevoflurane can sometimes cause convulsions or agitation in children and adolescents.

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

Today, general anesthesia is never performed with only one inhalation anesthetic. Anesthesia is now usually initiated by intravenous administration of the ultrashort-acting barbiturate thiopentone sodium or some other intravenous anesthetic; the patient loses consciousness almost instantly and enters the second phase of anesthesia. This allows an endotracheal tube to be inserted and then an inhalational anesthetic to be administered which further maintains the achieved depth of anesthesia (often two inhalational anesthetics are combined at a lower partial pressure to avoid their side effects). For better muscle relaxation (which is necessary for the successful work of the surgeon), the patient is given neuromuscular blockers; they allow the anesthesiologist to reduce the depth of anesthesia (this means that the risk of depression of the cardiovascular system will be lower) without making the surgeon's work more difficult. In order to prevent reflex activation of the autonomic nervous system due to pain, opioid analgesics (eg fentanyl) are added to the anesthetized patient. As stated at the beginning of this chapter, such anesthesia in which inhalation anesthetic is combined with other drugs is called "balanced anesthesia".

Malignant hyperthermia is one of the side effects of general inhalation anesthetics. Its cause is thought to be the uncontrolled release of C a $^{++}$ from the sarcoplasmic reticulum, which leads to muscle cell contraction, high energy consumption, heat generation and lactic acidosis. This dangerous condition is treated with dantrolene, a drug that prevents excessive release of C a++ 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 injecting into a vein, they reach the CNS within seconds and reach high concentrations in the brain tissue, which, due to its excellent blood supply, receives as much as ¼ of the minute volume of the heart. That is why 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 ***redistribution occurs*** , i.e. returning the drug from the brain tissue to the blood, and then moving from the blood to less well-perfused tissues (muscle and fat).

Although their effect lasts 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 important if these drugs are applied in a single dose, or for a short time, just to put the patient under general anesthesia; but, if they were to be used in the form of intravenous infusion, for a longer time, to introduce and maintain anesthesia during the entire surgical intervention, there is a possibility of accumulation in the body and delayed awakening of the patient after stopping the administration of drugs. However, by precise dosing of intravenous anesthetics through intravenous infusion (today there are computer programs that can accurately calculate the required dose and speed of administration), it is possible to avoid excessive accumulation of these drugs, and to maintain anesthesia enough to perform shorter surgical interventions or painful and unpleasant procedures. This type of anesthesia is called total intravenous anesthesia, which is especially popular today for ambulatory surgical interventions.

Ultra-short-acting barbiturates

Ultrashort-acting barbiturates include thio-pentone sodium, methohexital sodium, and thiamylal sodium. They are mostly used to **introduce** patients to general anesthesia, and much less often to maintain anesthesia during short interventions, or to deepen anesthesia caused by other means. The good properties of ultra-short-acting barbiturates are: quick and pleasant introduction to anesthesia, rarely causing vomiting, and the fact that there is no sensitization of the myocardium to catecholamines, nor an increase in secretion in the respiratory tract. Adverse effects of these drugs include myocardial depression and dilatation of the venous system (resulting in decreased cardiac output), respiratory depression, and sometimes laryngospasm.

Of the three mentioned barbiturates with ultra-short action, only methohexital stands out, due to its half-shorter action than the others, and less tendency to accumulate in the body during prolonged use.

Benzodiazepines

Midazolam is used the most for intravenous anesthesia, primarily because of its short action and solubility in water (the intravenous preparation contains water as a solvent, so it does not irritate the vein wall during injection). Midazolam, unlike other intravenous anesthetics, is quickly metabolized in the liver, so its half-elimination time is only 1-2 hours.

Midazolam is primarily used for ***conscious sedation***, which is required for shorter, unpleasant interventions. The patient does not lose consciousness completely, and can respond to verbal commands, while at the same time tolerates unpleasant and painful procedures (eg bronchoscopy, dressing, etc.). Midazolam with the correct dosage does not lead to depression of the heart or breathing, which is an additional advantage with anterograde amnesia (the patient later does not remember the unpleasant procedure he underwent).

The development of a new benzodiazepine anesthetic, remimazolam, is underway, the effect of which starts even faster, lasts less, and subsides more quickly than the effect of midazolam.

Propofol

Propofol is a short-acting intravenous anesthetic that is rapidly metabolized in the liver and other tissues to inactive metabolites. It is used for induction of anesthesia, for maintenance of anesthesia together with opioids, for conscious sedation and as an adjunct to general inhalation anesthesia. The good side of propofol is its antiemetic effect.

Propofol depresses heart rate and breathing, leading to hypotension; however, reflex tachycardia does not occur, because the baroreceptors are also inhibited. In addition, the use of propofol can 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.

Etomidate

Compared to barbiturates and propofol, etomidate is ***a safer*** drug to use, because it does not lead to a significant depression of the heart or breathing, with a slight expansion of the coronary arteries. And it, like propofol, is metabolized relatively quickly in the liver (half-elimination time of about 3 hours), so it does not tend to accumulate with prolonged use. It is used to introduce patients to anesthesia, and as an adjunct to anesthesia caused by other means.

The downsides of etomidate are the appearance of myoclonic attacks 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 a sufficient amount of hormones (due to the pyrrole ring in the etomidate molecule).

Ketamine

Ketamine is an intravenous anesthetic chemically similar to the psychotomimetic phencyclidine, which does not have a depressing effect on heart rate and arterial pressure. There is even a transient increase in blood pressure and an acceleration of the heart's work, due to the stimulation of the sympathetic nerves. Respiratory depression occurs only when using very high doses.

Ketamine-induced anesthesia resembles a trance state (eg, patient appears awake, eyes open, unresponsive to stimuli) and is accompanied by increased muscle tone (also resembles catatonia). Pharyngeal and laryngeal reflexes are also preserved. Ketamine's pronounced analgesic effect is particularly significant.

Its use is indicated in children and the elderly, whose cardiovascular system is particularly sensitive to the use of CNS depressors. 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 the possibility of intramuscular administration.

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

When it comes to side effects, ketamine causes nightmares and an unpleasant feeling of detachment from one's own body after waking up. That 's ″why ketamine anesthesia is called ″dissociative ″anesthesia ″. Sometimes patients are restless, crying and shouting. Fortunately, these effects are less common in children and the elderly than in other age groups.

Intravenous anesthesia with opioids

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

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

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

PHARMACOLOGY OF THE 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 pressure 130-139 mmHg), hypertension in stage **1** (diastolic pressure 90-99 mmHg , systolic pressure 140-159 mmHg) and hypertension in **stage 2** (diastolic pressure > 100 mmHg , systolic pressure > 160 mmHg). Hypertension must be treated because it leads to serious complications on the heart, kidneys and fundus.

When there is prehypertension, no medication is needed; hypertension in stage 1 is treated with the use of one drug, and hypertension in stage 2 with the use of combinations of drugs.

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

A decrease in 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** $_2$ presynaptic αreceptors in the cardiovascular center of the medulla oblongata (alpha-methyldopa only after it is converted into an active form in the body, α-methylnoradrenaline), 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 to be ineffective, as they have a lot of side effects.

Both drugs, by reducing sympathetic activity, reduce peripheral resistance to blood flow and cardiac output. At the same time, they do not reduce blood flow through the kidneys, nor glomerular filtration, which makes them useful drugs for hypertension in patients with reduced kidney function. However, after prolonged use, they lead to water and sodium retention; therefore, in principle, they are not used alone, but in combination with diuretics.

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

Alpha-methyldopa and clonidine cause sedation and drowsiness, dry mouth, nasal congestion, orthostatic hypotension, depression and impotence. In addition, alpha-methyldopa sometimes causes hemolytic anemia, thrombocytopenia, or leukopenia. Clonidine causes both constipation and nausea. The use of clonidine must not be stopped suddenly, because a sudden worsening of hypertension can occur (patients should be specially warned about this fact!).

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 noradrenaline depots in nerve endings (eg reserpine), and others reduce noradrenaline synthesis (metyrosine).

Guanethidine is taken up in the endings of adrenergic neurons by the same mechanism by which noradrenaline is taken up. In the very endings, it then prevents the release of noradrenaline, at the moment when the action potential reaches its end. Guanethidine is used to treat severe hypertension that does not respond to other medications.

Reserpine blocks the transport of noradrenaline and dopamine from the cytoplasm to presynaptic vesicles, which is why they are broken down under the action of monoamine oxidase. The end effect is a decrease in the amount of neurotransmitters and a weakened transmission in the sympathetic nervous system, as well as in the dopaminergic and noradrenergic pathways in the brain. Reserpine was once used as a medicine 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 congestion of the nasal mucosa, impotence, increased gastric acid secretion and diarrhea (due to predominance of the parasympathetic).

Metyrosine (alpha-methyl tyrosine) blocks the enzyme tyrosine-hydroxylase, thus preventing 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 congestion of the nasal mucosa.

Peripheral sympathetic blockade is also achieved by using **β-blockers or α-blockers.** Beta-blockers (propranolol, metoprolol) reduce the cardiac output and the release of renin in the kidney, which leads to a decrease in peripheral resistance due to a decrease in the level of angiotensin 2 in the blood. They are mostly used for the treatment of hypertension in younger people with a healthy myocardium.

Due to its negative inotropic and negative dromotropic effect, in larger doses in elderly people with a diseased heart, 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 on the extremities, because by blocking β-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 unwanted effect of vasodilators: reflex tachycardia.

Alpha blockers (primarily selective α_1-blockers, prazosin , terazosin are used and urapidil) lead to vasodilatation of arteries and arterioles, a drop in peripheral resistance and a drop in blood pressure. Also, due to the blockade αof -receptors in the walls of venules and veins, the inflow of venous blood into the heart, and thus the stroke volume, decreases. Although much less often than non-selective αβ-blockers, these drugs can also lead to reflex tachycardia due to a decrease in baroreceptor activation in the aortic arch and carotid sinus. In addition, they disrupt 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. To the patient who is prescribed prazosin, the doctor must explain that he should first start with a small dose (1 mg), which he should take immediately before going to bed; if he does not do so, strong 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 upside 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 prevent reflex tachycardia.

Urapidil is the only drug from 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 reduction is achieved by using diuretics, most often **thiazides or Henle's loop diuretics**. This effect is transient, so after a few weeks the intravascular volume returns to the initial level. However, the hypotensive effect lags behind, probably due to the direct vasodilatory effect of diuretics. Diuretics are commonly used to treat mild hypertension in the elderly. When they are applied, 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 kidney failure, only diuretics of the loop of Henle should be used, because then thiazides are not effective.

The drugs cause vasodilatation directly or indirectly. Minoxidil, hydralazine, diazoxide and calcium channel blockers act directly on arteries and arterioles; ni-troprusside-sodium acts on both arteries and veins. Vasodilators are used to treat moderate and severe hypertension, but only with diuretics (if used alone, they lead to fluid retention due to reduced blood flow through the kidneys). It is preferable to apply a beta-blocker at the same time, which would prevent the occurrence of reflex tachycardia; due to strong vasodilatation, baroreceptor activity decreases, so application of only vasodilators is followed 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 side of all vasodilators is the fact that they are always active, regardless of the mechanism of hypertension

In addition to reflex tachycardia, minoxidil causes congestion of the nasal mucosa and headache. It also enhances hair growth, which can result in increased hair loss in women. This effect on the hairs has been used to create various lotions (which include minoxidil as an ingredient) that promote hair growth in baldness.

Hydralazine is another orally administered vasodilator. It works by opening potassium ion channels in the smooth muscle cell membrane, and releasing nitric oxide from the endothelial cells (which then relaxes the smooth muscle).

Hydralazine is well absorbed after oral administration. It is metabolized in the liver, first by hydroxylation, then by glucuronidation and acetylation. Most of the drug goes through the process of acetylation, which is carried out 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 the amount of the enzyme that performs acetylation is too small. In such people (so-called "slow acetylators"),

hydralazine is eliminated much more slowly, so its effect is prolonged and enhanced. 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.

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

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. That's why it acts favorably both in hypertension and in acute heart failure. Sodium nitroprusside is used for the treatment of hypertensive crisis in the form of i.v. infusions. It breaks down spontaneously in the blood, so that its effect quickly stops; 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 stopping the infusion, the effect of the drug disappears in 2-3 minutes.

A special problem with the application of sodium nitroprusside is the accumulation of cyanide and thiocyanate, which are created by the decomposition of this drug. Cyanides lead to metabolic acidosis, dyspnoea, headache and loss of consciousness. Thiocyanates can cause delirium. In order for this not to happen, the infusion rate should not exceed 10 μg / kg / min.

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

Diazoxide is administered intravenously to treat hypertensive crisis. After application, the hypotensive effect starts in 5 minutes and lasts up to 12 hours. Since the use of diazoxide will cause a reflex activation of the sympathetic nerves, people with coronary disease should be given a beta-blocker at the same time, which will prevent the action of the sympathetic nerves on the heart.

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

Calcium channel blockers (amlodipine, nifedipine, diltiazem) are used as vasodilators to treat mild hypertension. They are well tolerated. Nifedipine can also be used to treat milder forms of hypertensive crisis. Then 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 receptors for angiotensin 2, and drugs that inhibit the action of renin. Medicines that inhibit convertase are called angiotensin-converting enzyme inhibitors, or ACE inhibitors for short. This enzyme is located in the endothelium of the lungs and converts angiotensin 1 to angiotensin 2, one of the strongest vasoconstrictor substances, and also breaks down bradykinin (a peptide with pronounced vasodilator action). Due to the decrease in the level of angiotensin 2 and the increase in the level of bradykinin after the administration of captopril, enalapril, ramipril, lisinopril, quinapril and other drugs from this group, there is vasodilation, a decrease in peripheral resistance and a decrease in blood pressure. These drugs also increase the cardiac output by reducing both the pre- and afterload of the heart; the thickness of the myocardium also decreases, i.e. hypertrophy recedes.

Captopril is administered orally. The hypotensive effect starts after 15 minutes, reaches its 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 the condition that the presence of renal artery stenosis is previously ruled out; if stenosis exists, convertase blockers can cause acute renal failure. In addition to treating hypertension, convertase blockers are also used to treat heart failure. They are combined with thiazide diuretics, because such a combination, in addition to the additive effect on heart failure, has another advantage: thiazides lead to hypokalemia, and ACE-inhibitors tend to raise the level of potassium in the serum, so the concentration of potassium remains within normal limits.

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

Captopril, as an older preparation, has several side effects: it causes neutropenia, metallic taste, edema and worsens asthma. Enalapril, ramipril, cilazapril, quinapril, fosinopril and other newer preparations do not have a toxic effect on the bone marrow. Due to the blockade of the synthesis of angiotensin 2, the synthesis of aldosterone 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 coughing).

ACE-inhibitors can cause pronounced hypotension at the first doses, so treatment is always started with smaller doses. 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 accumulation of bradykinin), ACE-inhibitors should not be used in persons with congenital or idiopathic angioedema.

Also, ACE-inhibitors should not be used in pregnant women, because they are teratogenic and fetotoxic.

Recently, AT_1 receptor blockers for angiotensin 2, losartan, valsartan, telmisartan, eprosartan, candesartan and irbesartan have also been used for the treatment of hypertension and heart failure. For now, these drugs are given only *to patients who were previously successfully treated with convertase blockers, but had to stop the therapy due to persistent cough*. Their proper place in therapy has yet to be established. In one of the clinical studies, 150 mg /day of irbesartan after 6 weeks led to a mean reduction of systolic/diastolic pressure by 10/5 mmHg. Adverse effects of these drugs are hypotension, hyperkalemia and angioedema. They

should be used with caution if there is stenosis of the renal arteries! (see convertase inhibitors!) Also, they are contraindicated during pregnancy, due to their teratogenic and fetotoxic effects.

All AT1 receptor blockers are administered orally. Losartan and candesartan are transformed in the liver into active metabolites, 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 not behind ACE-inhibitors, beta blockers, diuretics and calcium channel blockers in terms of effectiveness in the treatment of hypertension. It can be used alone or in combination with diuretics, beta blockers or calcium channel blockers. It is administered orally, once a day. A frequent side effect of aliskiren is hyperkalemia, and sometimes **deterioration of kidney function can occur** , especially in people who are hypovolemic, have diabetes, liver disease, or already damaged kidney function. Also, aliskiren can cause angioedema.

Aliskiren is poorly absorbed from the digestive tract (bioavailability is 2-3%), but penetrates well into tissues. Most of it is excreted unchanged through the stool, and about 1.4% of the orally administered dose is metabolized by cytochrome CYP 3 A 4. The half-elimination time of aliskiren is about 40 hours, which allows it to be used in one daily dose.

Choice of antihypertensive drugs

The choice of antihypertensive drugs depends primarily on the characteristics of each individual patient: associated diseases or conditions in the patient that affect the effectiveness and side effects of the drugs must be respected.

Mild hypertension (stage 1) is usually treated with one drug; moderate to severe hypertension (stage 2) is treated with a combination of two or more preparations that work by different mechanisms.

Treatment of hypertension in special types of patients

In elderly people, antihypertensive drugs should be used if diastolic pressure is higher than 90 mmHg or systolic pressure is higher than 160 mmHg during 6 months of observation. The drugs of choice for elderly patients are thiazide diuretics; if no effect is achieved, β-blockers are added.

In insulin-dependent diabetics, the drugs of choice for the treatment of hypertension are ACE-inhibitors, because they slow down the progression of nephropathy. ACE-inhibitors are even given to patients with diabetes type 1 who have normal blood pressure, provided that there is proteinuria. Diabetics with type 2 disease can be successfully treated with thiazides, ββ-blockers, calcium channel blockers or ACE inhibitors.

In case of renal insufficiency, thiazide diuretics often do not work, so it is necessary to use a diuretic of Henle's loop.

During pregnancy, the drug of choice for the treatment of hypertension is methyl-dopa, as it carries the lowest risk of congenital anomalies. Apart from that drug, nifedipine can be used; β- blockers can only be used in the first trimester of pregnancy. We use hydralazine to treat spikes in blood pressure as part of preeclampsia.

Treatment of hypertensive crisis

A sudden jump in blood pressure can be without symptoms, when such a condition is called a " *hypertensive emergency* ", or it is accompanied by neurological symptoms or acute damage to the heart or kidneys, when such a condition is called a " *hypertensive crisis* ". A hypertensive emergency can be treated outside the hospital by oral administration of ACE inhibitors (eg captopril 25 milligrams) or labetalol (200-400 milligrams). These drugs act for a relatively short time, so chronic therapy should be started after lowering the pressure. No one should try to lower blood pressure suddenly, to normal values, because this can do more harm than good. A sudden drop in blood pressure can lead to ischemia of vital organs and symptoms.

A patient with a hypertensive crisis should be hospitalized immediately, preferably in the intensive care unit, and parenteral antihypertensives should be administered: sodium nitroprusside, labetalol or urapidil.

Table 10 . Doses of the most commonly used antihypertensive drugs

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Propranolol	orally	80 mg	12 o'clock
Methyldopa	orally	500 mg	12 o'clock
Prazosin*	orally	3 mg	8 hours
Nifedipine	orally	10 mg	8 hours
Hydralazine	orally	10 mg	6 o'clock
Enalapril	orally	2.5 mg	12 o'clock

diazoxide**	i.v.	100 mg	15-30 minutes, the total dose should not exceed 300 mg
Sodium nitroprusside**	i.v. infusion	1-5 μg / kg / min	The infusion bottle and system must be dark colored as this medicine is sensitive to light

* The first dose must be small (1 mg), and is taken immediately before going to bed due to the risk of excessive hypotension.
** It is 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 dyspneic on exertion; over time, due to high pressure in the pulmonary artery, right ventricle insufficiency occurs. Without treatment, patients can live only a few years. In most patients, the serum level of endothelin 1, a peptide paracrine factor that leads to vasoconstriction, is elevated.

are used to treat pulmonary hypertension : endothelin 1 receptor blockers, drugs that increase the concentration of cyclic guanosine monophosphate (cGMP) and prostaglandin analogues.

Three endothelin receptor blockers are currently in use: **bonsetan**, which non-selectively blocks endothelin A and B receptors, and **ambrisentan and macitentan**, which selectively blocks it. mainly endothelin A receptors. Previous experiences with bonsetan have shown that it should be used in primary pulmonary hypertension and pulmonary hypertension caused by scleroderma. The drug reduces dyspnea, patients are able to move longer, and exacerbations are less frequent. Four years after the introduction of bonsetan in therapy, about 85% of patients survive. It is administered orally.

Side effects of bonsetan are serious: 11% of patients have elevated transaminases, and 6% of patients develop anemia. Hypotension, reddening of the skin and palpitations occur in some patients.

The advantage of ambrisentan and macitentan is in their selectivity for A receptors, because the activation of endothelin B receptors leads to the creation of vasodilators nitrogen monoxide and prostacyclin. However, their effects in clinical studies were very similar to those of bonsetan. It is administered orally, and it has similar side effects as bonsetan: it increases the level of transaminases, causes anemia and leads to the formation of peripheral edema. However, macitentan appears to have slightly less hepatotoxicity than the other two drugs.

Of the drugs that increase cGMP concentration, inhibitors and phosphodiesterase type 5 were first used: **sildenafil and taladafil** . They reduce dyspnoea and allow longer movement of the patient, but there is no evidence yet that they affect the length of survival. They have the advantage of oral administration and weak side effects. Recently, a drug that directly stimulates guanylate cyclase to create more cGMP has entered therapy: **riociguat**. Riociguat has been shown to be more effective than phosphodiesterase inhibitors, as it increases patients' quality of life and enables longer mobility. The only serious side effect of this drug observed so far is an increased frequency of hemoptysis. Riociguat is administered orally.

Prostacyclin analogue, **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. Among the side effects, iloprost causes hypotension, cough, headache, and rarely bronchospasm and bleeding from peptic ulcer.

Epoprostenol is a prostaglandin produced by endothelial cells. Epoprostenol inhibits the aggregation of platelets and acts as a vasodilator 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. Side effects include headache, facial flushing and thrombocytopenia.

DIURETICS

Diuretics are drugs that increase the excretion of mo-shorter, and which are applied with the aim of removing excess extracellular fluid, together with its electrolytes. According to the 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 tubular secretion system), reach the distal tubules, and there block the reabsorption of Na + and Cl - ions (the so-called ^{co} - transport of sodium ^{is} blocked and chlorine). These ions drag water with them, which results in an increase in the amount of urine. In an attempt to retain as much sodium as possible, the end parts of the distal tubules and the collecting ducts exchange ^{Na} $^{+}$ ions for K $^{+}$ ^{ions} , so that thiazide administration leads to hypokalemia. Thiazides are used to treat mild edema (in heart failure, cirrhosis, etc.) and mild hypertension. Since they reduce the secretion of calcium in the kidney, they can also be used to treat renal calculus. 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 the

same as thiazides. In addition to hypokalemia, the side effects of these drugs include hyperglycemia, hyperlipidemia, and hyperuricemia. Exceptionally, indapamide does not cause hyperglycemia.

The maximum effect of thiazide diuretics (which is achieved with maximum doses), in terms of the amount of urine, reaches about 5% of the ultrafiltrate, i.e. fluid that is filtered in the glomeruli. This practically means that they can increase urine output by just a few liters.

Thiazide and similar diuretics are quickly absorbed after oral administration, and start to have a visible effect after one hour. Most of them are eliminated in the urine, but a part of the ingested dose is excreted in the bile, using the mechanism for the secretion of bile acids; this route of elimination becomes particularly significant in case of kidney failure. The effect of thiazide diuretics lasts on average up to 12 hours, so most of these drugs are administered in one 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 improve the patient's condition to some extent.

Loop of Henle diuretics. Drugs from this group (furosemide, bumetanide, torsemide and ethacrynic acid) are also secreted in the proximal tubule, but act on the ascending, thick arm of the loop of Henle, preventing the reabsorption of N a + , K + and Cl - . They inhibit the transporter that reabsorbs together one Na + ion, one K + ion and two Cl - ions . As much as 20% of the sodium filtered in the glomeruli is reabsorbed by this transporter.

Loop of Henle diuretics are significantly more effective than thiazides. They are used for the treatment of severe edema, for moderate and severe hypertension, for the treatment of pulmonary edema due to left heart failure and for the treatment of hypercalcemia (because they reduce the reabsorption of C a ++) with the use of saline infusion. Sometimes these diuretics, if administered early enough, can prevent the onset of acute renal failure due to hemoglobinuria (eg in transfusion reactions) or myoglobinuria (in crash syndrome). By increasing the flow of primary urine through the tubules, they can "wash out" at least part of the hemoglobin and myoglobin from the kidneys and prevent blockage of the tubules. Loop of Henle diuretics cause hypokalemia, transient hearing loss (if administered too rapidly intravenously), hyperuricemia (increase in uric acid levels), and hyperglycemia. Only ethacrynic acid (whose molecule has no similarity with other diuretics from this group and sulfonamides) does not cause hyperglycemia. If they are overdosed, severe hypotension and loss of consciousness occur due to electrolyte imbalance.

Unlike thiazides, loop of Henle diuretics can also work in people with kidney failure.

All diuretics from 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 6-7 hours. A high percentage of them are bound to plasma proteins. They are mostly excreted in the urine by tubular secretion; one third of the drug dose is excreted in the bile. Loop of Henle diuretics are not metabolized in the liver to any significant extent.

Carbonic anhydrase inhibitors. Acetazolamide and drugs similar to it (methazolamide, dichlorphenamide) inhibit the enzyme carbonic anhydrase, which enables reabsorption of bicarbonate in the proximal tubules. Bicarbonates remain in the lumen of the tubules, pulling Na + ions and water molecules and leading 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 primarily used 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 are hyperchloremic acidosis, hypokalemia (in addition to inhibition of carbonic anhydrase, the reabsorption of potassium ions in the distal tubule and collecting ducts decreases) and neurological disorders (paresthesias, confusion, ataxia, tingling in the extremities, loss of appetite).

Potassium-sparing diuretics. Medicines from 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 receptors for aldosterone, the hormone of the adrenal cortex responsible for resorption of N a + and excretion of K + (spironolactone and eplerenone), or by blocking channels for N a + in the collecting ducts (triamterene and amiloride). Potassium-sparing diuretics also inhibit the secretion of hydrogen ions (N +) in the collecting ducts.

Spironolactone is used to treat primary (Kohn's syndrome) and secondary hyperaldosteronism (in liver cirrhosis, nephrotic syndrome and congestive heart failure). Triamterene and amiloride are used when there is a risk of hypokalemia due to previous use of thiazides or loop of Henle diuretics; medicinal preparations containing a combination of thiazide diuretics and triamterene or amiloride are often used right from the beginning of therapy, which prevents the occurrence of hypokalemia.

Adverse effects of these diuretics are hyperkalemia, metabolic acidosis (because inhibition of N a + reabsorption reduces excretion except for K + and N +) and neurological disorders (paresthesias, depression). Spironolactone also blocks androgen receptors, so it can cause gynecomastia and impotence in men, and menstrual cycle irregularities in women. Eplerenone is significantly less likely to cause gynecomastia and impotence.

Osmotic diuretics. Osmotic diuretics are substances that, after administration, are filtered through the glomeruli of the kidneys and then not reabsorbed from the lumen of the renal tubules. Remaining in the tubule lumen, osmotic diuretics increase the osmolarity of primary urine and thus prevent water reabsorption. The result is the excretion of a large amount of dilute urine.

Table 11. Doses of the most commonly used diuretics

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Hydrochlorothiazide	orally	50 mg	12 o'clock
Indapamide	orally	2.5 mg	24 hours
Furosemide	i.v.	20 mg	12 o'clock
	orally	40 mg	12-24 hours
Amiloride	orally	10 mg	24 hours
Spironolactone	orally	100 mg	24 hours
Acetazolamide	orally	250 mg	12 o'clock
Mannitol	20% solution, i.v. infusion	12.5 years	*

* First, a test dose of 12.5 g is applied; if in the next 3 hours the diuresis increases to 50 ml / h or more, then another 12.5 g can be applied.

Today, mannitol is mostly used as an osmotic diuretic (once upon a time, glycerol, isosorbide and urea were also used; 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; sleep is effective only if applied early enough, while there is still some diuresis. By ensuring the flow of primary urine through the tubules, this drug prevents tubular cell necrosis.

Mannitol can also lower raised intracranial pressure (eg in brain edema) and raised 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.

Recombinant human B-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. Sa $^{++\ \text{enters}}$ these cells through protein structures in the membrane that we call calcium channels. The largest number of calcium channels are activated (opened) when the cell membrane is depolarized. That's why we say they are voltage-dependent channels. There are several types of voltage-dependent channels for calcium: L (they are the most numerous, they got their name from the English word *large* = wide, large, because after activation they are wide and long open), T (they are 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). Blockers of calcium channels 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 blockers, designated by Roman numerals: site I , where 1,4-dihydropyridines bind, site II , where verapamil and similar drugs bind, and site III , where diltiazem binds. Due to different binding sites, individual calcium channel blockers differ from each other in their mechanism of action and end 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 such a phenomenon lies in the easier binding of these drugs to calcium channels that are either open or inactivated (a condition that immediately precedes the closing of the channel).

There are three basic chemical groups of these drugs: 1) **verapamil** and similar 2) **1,4-dihydropyridines** (nifedipine, nimodipine, nicardipine, felodipine, amlodipine, nisoldipine, isradipine) 3) **dibenzothiazepines** (diltiazem). Blockers of calcium channels act primarily on the heart and smooth muscles of arterial blood vessels. They have a depressing effect on the heart: they reduce conduction speed in the A- V node, reduce the force of cardiac contraction, reduce irritability and heart rate. On the other hand, they dilate mainly arterial blood vessels and lead to a decrease in blood pressure. Verapamil primarily acts on the heart, and weakly on the blood vessels; dihydropyridines primarily dilate arterial blood vessels and have a weak effect on the heart. Diltiazem acts equally on the heart and blood vessels.

Verapamil is used to treat atrial arrhythmias (can interrupt or prevent the occurrence of paroxysmal supra-ventricular tachycardia), angina pectoris (angina on exertion and vasospastic angina), Raynaud's syndrome (functionally impaired blood flow in the hands and feet) and hypertension. Other calcium channel blockers are used only for the treatment of hypertension, Raynaud's syndrome and angina pectoris (because by reducing blood pressure, they reduce the workload of the heart and the consumption of oxygen in the myocardium, 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 also 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 passage, 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-elimination time is around 5-8 hours, they must be applied 2-3 times a day.

Calcium channel blockers are well tolerated. Rarely, mild side effects occur in the form of headache, facial redness and leg swelling at the level of the malleolus. Verapamil may cause constipation in elderly patients. In principle, calcium channel blockers should not be given together with -adrenergic receptor blockers β. 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) can lead to complete A-V block). Also, calcium channel blockers should not be given to people with heart failure because they can worsen it due to the weakening of the strength of heart contraction. Calcium channel blocker overdose results in hypotension, bradycardia, and/or A-V block.

When it comes to nifedipine, you should avoid using doses higher than 20 mg at once, because sudden vasodilation, drop in blood pressure and reflex tachycardia occur; if the patient already has coronary disease, a myocardial infarction may occur!

Nimodipine and flunarizine stand out for their selectivity. They act mostly on the blood vessels of the brain and brain. That's why nimodipine is used in subarachnoid hemorrhage to prevent accompanying spasm of these blood vessels, and flunarizine can prevent and suppress migraine attacks. Amlodipine differs from other 1,4-dihydropyridines in its more gradual onset and cessation of action, which facilitates clinical application.

Several years ago, a serious interaction of calcium channel blockers (primarily amlodipine, diltiazem, felodipine, nifedipine and verapamil) with the antibiotic ***clarithromycin was discovered.*** If clarithromycin is prescribed to patients on chronic therapy with one of the mentioned calcium channel blockers due to an infection, it strongly inhibits cytochrome 3A4 and thus prevents the metabolism of calcium channel blockers, increasing their blood concentration up to five times. The patient then falls into severe hypotension, which leads to acute renal failure.

Table 12. Doses of the most important calcium channel blockers

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Nifedipine	orally	10 mg	8 hours
Verapamil	orally	160 mg	8 hours

NITRATES

Nitrates are the drugs that have a nitrate group (NO3) 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, leads to accumulation of cyclic guanosine monophosphate and relaxation of smooth muscle cells. Cyclic guanosine monophosphate is thought to induce relaxation due to inhibition of calcium release from the sarcoplasmic reticulum and inhibition of calcium entry into the cell through L -type calcium channels in the cell membrane. Today, the most commonly used nitrates in clinical practice are nitro-glycerol, pentaerythritol-tetranitrate, isosorbide mono- and di-nitrate.

These drugs relax all smooth muscles, but they are used primarily for the dilation of venous blood vessels. As a result of this effect, blood accumulates in the veins and thus the flow to the heart is reduced (ie, the so-called preload of the heart is reduced*)*. The heart now works less and consumes less oxygen. If nitrates were taken by a patient with narrowed coronary arteries who had chest pain attacks (arteriosclerotic angina pectoris), 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. 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 quickly reduced in the liver to inactive metabolites so that their half-elimination time (and thus the effect) is very short (eg half-elimination time of nitro-glycerol = 3-8 minutes). In order to extend the duration of their effect, they are administered either sublingually (nitroglycerol), because after absorption they do not pass through the liver immediately, or in the form of delayed-release tablets (other nitrates), which release the drug in the intestines over a longer period of time and thus "compensate" a drug that has already decomposed after absorption. Recently, nitroglycerol is applied transdermally, using a special patch that gradually releases the drug and thus maintains constant concentrations of nitroglycerol in the blood for 24 hours.

After applying nitroglycerol under the tongue, the effect starts in 2-5 minutes, and the maximum effect is achieved in about 10 minutes. After 20-30 minutes, the effect is completely lost. When applying nitroglycerin under the tongue, 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 compounds resulting from their further metabolism, are water-soluble, and are excreted through urine.

A special problem with nitrate therapy is the emergence of tolerance to their effect. Tolerance develops quickly, already within one day of continuous application. However, since tolerance is lost just as quickly after discontinuation of the drug, intermittent use

of nitrates is advised. Namely, they should be applied during the day and not at night; thus the tolerance created during the day will be lost during the night. Intermittent administration of nitrates is not without danger: early in the morning, before administration of a new dose of nitrates, the concentration of the drug in the blood is practically unmeasurable, so the patient may get an angina pectoris attack, especially if he gets up suddenly or gets excited. Such a phenomenon is called the " **zero hour effect** ", and the patient should pay attention to it.

The side effects of nitrates are mild and are a consequence of their basic effect on blood vessels. Due to vasodilatation of the blood vessels in the neck and head, headache and redness of the face and neck occur, and due to excessive dilation of veins and excessive reduction of venous inflow to the heart, tachycardia and hypotension may occur. Nitrates increase intracranial pressure due to expansion of neck and head veins, so they should not be given to people who are at risk of swelling of the brain tissue (injuries, tumors, brain infarction, bleeding in the brain, etc.).

Nitrites are similar to nitrates, the compounds that instead of nitrate have a nitrite group (NO_2) in their molecule. The most used representative of nitrite is amyl nitrite, a highly volatile substance that was administered by inhalation. Today, nitrites are rarely used because with prolonged use they lead to significant methemoglobinemia (oxidize Fe^{2+} hemoglobin to Fe^{3+}), which is manifested by pseudocyanosis. Nitrates cause methemoglobinemia much less frequently, but if they are administered orally in large doses, part of that dose is converted into nitrites under the action of 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 precisely to induce methemoglobinemia in patients poisoned with cyanide. Methemoglobin binds to itself the cyanide ion, thus reducing its toxicity.

In patients on nitrate therapy, the use of phosphodiesterase type 5 inhibitors (sildenafil, taladafil, vardenafil) is contraindicated, as severe hypotension, decreased coronary perfusion and myocardial infarction may occur.

Table 13. Doses of nitrates

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Nitroglycerol	sublingually	0.5 mg	to stop an attack of angina pectoris
	i.v. infusion	10-100 μg / min	-
	transdermally	15 mg per patch	24 hours
Pentaerythritol tetranitrate	orally	10 mg	6 hours
The isosorbide-dinite war	orally	10 mg	6 hours

POTASSIUM CHANNEL ACTIVATORS

Nicorandil is a drug that opens channels for potassium, leading to 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. Nicorandil is used in the second line of therapy (when beta-blockers and nitrates are no longer effective or cannot be used for some reason), mostly alone, but can be added to patients already receiving maximal 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 an aorto-coronary bypass surgery.

Because of the risk of excessive hypotension and reduced blood flow to the heart, nicorandil should be dosed cautiously. As with nitrates, simultaneous administration of nicorandil and phosphodiesterase type 5 inhibitors is contraindicated, as severe hypotension with myocardial hypoperfusion may occur. In the last few years, a serious side effect of nicorandil has been discovered: it causes ulcers on the skin (especially the perianal area) and mucous membranes, which sometimes lead to the formation of fistulas. After nicorandil administration is stopped, the ulcers heal spontaneously.

Pinacidil and cromakalim also open potassium ion channels, but have not been developed to the stage of becoming licensed drugs.

BETA BLOCKERS

The sympathetic nervous system exerts most of its stimulatory influence on the internal organs through β-receptors. Binding of catecholamines to β-receptors leads to: acceleration of the heart, strengthening of its contractility, acceleration of conduction and increased heart excitability (β_1 subtype); bronchodilation (β_2 subtype); stimulation of renin release from the cells of the juxtaglomerular apparatus (β_1 subtype); increased blood flow through skeletal muscles (β_2 subtype); increased release of insulin and relaxation of the uterus (β_2 subtype). By blocking βreceptors in the heart and on the cells of the juxtaglomerular apparatus, very favorable effects can be achieved in patients with hypertension, angina pectoris and arrhythmias. Propranolol, a non-selective blocker of both $_1$ and β_2 receptors, is mostly used for these indications.

β Beta blockers are used to treat hypertension in younger people with a 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 in practice 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 e.g. Verapamil is administered intravenously.

β blockers have a special place in the prevention of recurrence of myocardial infarction. If the use of atenolol and metoprolol begins in the acute phase of the heart attack, and acebutolol, propranolol and timolol in early convalescence, the possibility of a new heart attack is reduced to one 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 used for this indication.

In addition to all of the above, β-blockers are useful in the treatment of thyrotoxicosis and preparation of the thyroid gland for surgery. They are also used to prevent 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 passage, while the metabolism of others is much slower. Due to moderate absorption and the effect of the first passage through the liver, the bioavailability of most beta-blockers does not exceed 50%. The half-elimination time of most beta-blockers is relatively short (3-6 hours), while for some it reaches 24 hours (eg nadolol); therefore, most drugs from this group are administered several times a day.

Unwanted effects of propranolol and other beta blockers originate from blocking β-receptors in other tissues or the heart itself. Thus, it can lead to bronchoconstriction in asthmatics (blockade of β_2 receptors in the bronchi), to worsening heart failure and conduction block in the heart, to hypoglycemia (in small children, very old people and diabetics taking oral antidiabetics), to hypertriglyceridemia. and lowering of HDL -cholesterol, and to deterioration of flow through the extremities in patients with atherosclerosis. Due to penetration into the central nervous system and additional blocking effect on N a $^{+\text{ channels}}$, 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 β_1 antagonists (atenolol, metoprolol, betaxolol, bisoprolol and nebivolol) or by the use of β-blockers that have a certain stimulatory activity on β-receptors (so-called partial agonists: oxprenolol, pindolol and others)).

Due to the depressant effect on the myocardium and conduction block, β-blockers are contraindicated in patients with 2nd or 3rd degree A-V block.

All beta-blockers show similar clinical efficacy. The choice of medicine is based on differences in additional effects and side effects. Thus, oxprenolol, pindolol, acebutolol and celiprolol also have a sympathomimetic effect, which enables less bradycardia and better blood flow through the extremities (due to the stimulation of β_2 receptors in the blood vessels of the extremities). Atenolol, celiprolol, nadolol and sotalol are more polar substances than other β-blockers; therefore, they penetrate less into the CNS and cause less sleep disturbances and nightmares. Labetalol, celiprolol, carvedilol and nebivolol lead to vasodilatation, which may be useful in certain clinical situations. Carvedilol is a newer, non-selective beta-blocker that blocks alpha receptors in addition to beta receptors. Due to this additional effect, it does not cause a deterioration of the flow through the extremities, so it can be used in patients with peripheral arteriosclerosis. Carvedilol is also less likely to cause the metabolic side effects of beta blockers. Nebivolol does not cause hypertriglyceridemia and hypoglycemia, but may mask signs of hypoglycemia. Bisoprolol is a selective beta 1 blocker that has become very popular among cardiologists here in recent years, because it is eliminated in a way that greatly facilitates its application. Bisoprolol has so-called "balanced elimination", i.e. it is largely eliminated through the kidneys and liver. Therefore, the dose of bisoprolol does not need to be adjusted when the patient has renal or hepatic insufficiency.

When applying β-blockers, it is very important to know that ***the therapy must not be stopped suddenly***! If this is done, the heart suddenly becomes hypersensitive to the effects of the sympathetic nervous system (because in the meantime there has been an increase in the number of β_1 receptors, the so-called upregulation of receptors), so there may be increased oxygen consumption and anginal attacks, or even heart attacks. That's why long-term use βof -blockers requires their ***gradual*** abolition, by reducing doses over a period of several weeks.

Table 14. Doses of some beta-blockers

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Propranolol	Orally	80 mg	12 o'clock
Metoprolol	Orally	100 mg	24 hours
Pindolol	Orally	15 mg	12 o'clock

TREATMENT OF ANGINA PECTORIS

The treatment of angina pectoris and other manifestations of myocardial ischemia is based on two principles: (1) reducing the myocardial oxygen demand, and (2) increasing coronary flow through the potentially ischemic myocardium. Angina pectoris occurs

in three clinical forms, which require special therapeutic approaches. **Angina on exertion** or "classic" 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) is caused by spasm of the coronary arteries, and is usually not associated with physical exertion. **Unstable angina** pectoris is caused by reversible and recurrent blockage of the coronary artery by deposited platelets on the atherosclerotic plaque, which has ruptured towards the lumen of the blood vessel.

In classic 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 S T-segment depression on the ECG during physical exertion. Which drug will be chosen to prevent an attack of angina pectoris, depends on other characteristics of the patient. In patients with hypertension, it is most convenient to use beta-blockers or long-acting calcium channel blockers; in patients with normal arterial pressure, it is better to choose retard forms of nitrates. Of course, the cessation of attacks of classic angina pectoris is best achieved by sublingual administration of nitroglycerol.

Ivabradine blocks ion channels in cells of the sino-atrial node through which a mixed current of sodium ions and potassium ions passes. The result of its action is **the slowing down of the heart**, which saves energy and consumes less oxygen. 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 disorders of the sinus node, slow conduction of impulses in the heart or severe heart failure. Undesirable effects of ivabradine are severe bradycardia, ventricular extrasystoles, phosphenes (appearance of "fireflies" before the eyes), hyperuricemia and increase in serum creatinine.

Ranolazine and trimetazidine inhibit the enzyme 3-ketoacyl coenzyme A thiolase in the mitochondria of the myocardium, thereby reducing **beta-oxidation of fatty acids**. Because of this inhibition, myocardial cells reorient themselves to glycolysis, so they need less oxygen than usual (because glucose has more oxygen in its molecule than fatty acids). Trimetazidine and ranolazine are equal to beta-blockers and calcium channel blockers in terms of effectiveness in preventing attacks of stable angina pectoris. They can be used to prevent angina attacks alone or in combination with a beta blocker or calcium channel blocker. Side effects of these drugs include QT prolongation, gastrointestinal distress, visual disturbances, tinnitus, and mild swelling.

In case of classic angina pectoris, in addition to the already mentioned therapy, patients should be given small doses of acetylsalicylic acid (to prevent the formation of thrombus in the coronary atria) and lower the cholesterol level by using one of the drugs from the statin group (see later chapter).

Calcium channel blockers or nitrates can be used to both prevent attacks and stop attacks of vasospastic angina pectoris. These two groups of drugs can 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 case of 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 may be added. However, since the main pathological phenomenon in unstable angina is the formation of thrombus, antiplatelet (aspirin, ticlopidine or clopidogrel) and anticoagulant drugs (heparin, unfractionated or low molecular weight) should be introduced into the therapy. The patient must be monitored intensively, so that fibrinolytic therapy can be applied in case of complete occlusion.

CARDIOTONIC GLYCOSIDES

Cardiotonic glycosides (digoxin, digitoxin) are natural substances obtained by extracting from Digitalis lanata and Digitalis purpurea. At the end of the 18th century, the English doctor William Wiedering was the first to introduce Digitalis into official medicine, noticing that a herbalist (called a witch by local residents) successfully treated heart failure with a mixture of plants, among which was Digitalis.

Cardiotonic glycosides block Na^+, K^+, ATP - ase, the main transporter of ions in the membrane of most cells. As a result, there is a slight depolarization of the membrane, the opening of channels for the entry of calcium ions and the inhibition of the transport of Ca^{++} outside 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 sarco-plasmic reticulum. Myocardial cells now contract more efficiently: with the same energy expenditure, the contraction has a greater amplitude. This allows the heart that is sick to pump blood better, so the symptoms and signs of heart failure go away. At the same time, cardiotonic glycosides increase the activity of the parasympathetic (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 there is a marked clinical improvement in patients, 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 establish sinus rhythm) and supraventricular paroxysmal tachycardia. For this last indication (supraventricular tachycardia), a significantly more effective drug is used today - adenosine, in the form of an intravenous injection of 6 mg .

Cardiotonics are well absorbed from the gastrointestinal tract. Digoxin is very little metabolized in the liver, and is mostly eliminated unchanged via the kidneys ($t_{1/2}$ ~36 hours). After metabolizing in the liver, digitoxin is eliminated via bile ($t_{1/2}$ ~7 days). Both drugs can be administered orally and parenterally.

In order to achieve their effect, cardiotonic glycosides must reach a certain concentration in the blood and extracellular fluid. It is usually said that the patient is then digitized. The desired therapeutic concentration can be reached in two ways: (1) by the so-called gradual (slow) digitalization, when the patient receives a maintenance dose from the beginning (for digoxin it is 0.25 mg per day, orally), so that the therapeutic concentration is reached after about a week and (2) by the so-called rapid digitalization, when the patient receives a shock dose immediately (for digoxin it is 0.5 mg i.v. and or 0.75 mg orally) and then continue with the maintenance dose (for digoxin 0.25 mg daily, orally) so that the therapeutic concentration is reached immediately on the same day.

Due to the presence of Na^+, K^+, ATP-ase in most cells, cardiotonic glycosides have many side effects. They can be cardiac (A-V block, trough depression of the S -T segment, occurrence of ventricular extrasystoles; often each extrasystole is accompanied by a normal Q RS complex in the ECG - such a finding is called bigeminy) and extracardiac (nausea, vomiting- her, seeing a yellow halo around objects, psychosis).

In the event that cardiotonics are overdosed and true poisoning occurs, Fab fragments of antibodies that bind cardiotonics should be administered. The fragments bind to the cardiotonic and thus prevent its harmful effect on the cells.

NATRIURETIC PEPTIDES

Natriuretic peptides cause diuresis, natriuresis and vasodilation. The secretion of aldosterone and angiotensin 2 decreases. The result is a reduction in the load on the heart; this explains the increase in the level of these peptides in the serum of people suffering from heart failure. There are three peptides:

1. **A** (or atrial) natriuretic peptide, which is secreted by the atria in response to dilation
2. **B** natriuretic peptide, which is secreted by the chambers of the heart in response to the increase in pressure at the end of diastole
3. **C** natriuretic peptide, which is secreted by endothelial cells of blood vessels

BNP), which has 32 amino acids, called ***nesiri tid,*** is used as a medicine . It is indicated for the intravenous treatment of acute heart failure in patients who have dyspnea at rest. In them, nesiritide improves dyspnea and reduces the pressure in the pulmonary - capillaries.

Nesiritide must be dosed carefully to avoid excessive hypotension, which can worsen the patient's condition. That is why its use is contraindicated in patients with systolic arterial pressure lower than 90 mmHg. In patients whose renal function depends on the production of angiotensin 2 and the release of aldosterone, nesiritide may cause a rise 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. Elymes are removed from the circulation by the action of endopeptidases and filtration in the kidneys. Half-elimination time is 18 minutes.

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 a cornerstone in the treatment of heart failure, 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. Along with ACE-inhibitors, diuretics are often used, namely thiazides (if kidney function is normal) or loop diuretics (if kidney function is impaired). In more severe forms of the disease, it is even possible to combine both types of diuretics, or to add spironolactone, which has been shown to further reduce mortality. Constant monitoring of serum creatinine and potassium is necessary.

β- blockers bisoprolol, carvedilol and metoprolol can be used to treat stable heart failure, especially in left ventricular dysfunction. Their application starts with very small doses, which are carefully increased until the optimal effect.

Today, digoxin is 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.

If the patient is in **acute heart failure, milrinone** can be used , a drug that specifically blocks phosphodiesterase in the heart, leads to the accumulation of cAMP and an increase in the concentration of calcium in the cytoplasm. All the mentioned changes result in an increase in myocardial contractility and better relaxation of the chambers of the heart in diastole. Milrinone also leads to vasodilatation in the pulmonary circulation, as well as systemically, which further facilitates the work of the heart. It is administered parenterally, as an IV infusion. The main danger with the use of milrinone is the possibility of induction of ventricular arrhythmias, so strict monitoring of the ECG and concentration of ions in the serum is necessary.

TREATMENT OF MYOCARDIAL INFARCTION

The initial treatment of a myocardial infarction is carried out with the use of oxygen, morphine (in order to suppress pain), aspirin (300 mg, due to its anti-aggregation effect) and a thrombolytic drug (must be added within 12 hours after the onset of the infarction, ideally within the first 60 minutes). Along with the thrombolytic drug, heparin is used to prevent re-thrombosis. Nitrates

(to reduce pain), -blockers (atenolol, metoprolol) and ACE-inhibitors βare also used (use should be started in the first 24 hours after the heart attack, provided that arterial pressure is normal; use is then continued for 6 weeks).

Aspirin (75 mg /day), β-blocker (acebut o lol, metoprolol, timolol or propranolol if there is no left ventricular insufficiency, and Carvedi - lol, bisoprolol or metoprolol if left ventricular failure has occurred), ACE -inhibitor (if left ventricular failure), nitrates (if angina pectoris) and statin (for prevention of myocardial infarction).

Today, an increasing number of patients with acute myocardial infarction undergo urgent **percutaneous interventions** on the coronary arteries, which involve first coronary angiography to locate the narrowing of the arteries, followed by balloon dilatation of the site and insertion of a coronary stent (a metal tube with a mesh wall) that prevents further narrowing of the coronary artery. arteries. With these interventions, the issue of ischemia is solved mechanically, so the therapy is focused on the use of anti-aggregation drugs that should prevent thrombosis and clogging of the stent. During the intervention itself, the patient is given **abciximab**, a Fab fragment of a monoclonal antibody that binds to glycoprotein receptors IIb/IIIa , important for platelet adhesion (fibrinogen and von Willebrand factor bind to these receptors), while after the intervention, dual antiplatelet therapy (aspirin + another antiplatelet drug). This dual therapy must last at least one month if the stent is ordinary, metal, and at least one year if the stent is metal, but also made to release drugs from the group of immunosuppressants (which prevent endothelial proliferation and clogging of the stent in another way).

ANTIARRHYTHMICS

Arrhythmias represent a disturbance of the normal, sinus rhythm of the heart (around 70-80 beats per minute, with equal time intervals). An irregular heart rhythm 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, there 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 conducting system, any other heart cell can under certain conditions (hypokalemia, acidosis, ischemia) acquire the characteristics of spontaneously depolarizing cells. Then the cell with the fastest spontaneous depolarization becomes an abnormal conductor of the heart rhythm, i.e. focus of arrhythmia.

A special cause of arrhythmia due to disturbances in impulse generation is the occurrence of early and late post-depolarizations (early ones occur before the repolarization of the heart cell, and late ones only after full repolarization has occurred). Late post-depolarizations are a consequence of increased calcium concentration inside the cell, e.g. with prolonged use of cardiotonic glycosides.

Arrhythmias due to disturbances in impulse conduction imply the occurrence of a block in impulse conduction; the block can be **complete (bidirectional)**, when the impulses cannot spread further, or **unidirectional**, when the impulses in a part of the heart tissue *cannot spread in one direction*, but can in the opposite direction and that very *slowly*. When there is bidirectional block, arrhythmias known as SA block, AV block, or bundle branch block occur. When there is a unidirectional block, the depolarization wave propagates through normal tissue, while it decays rapidly in the blocked tissue. However, when the depolarization wave bypasses the blocked site, it begins to propagate through it from the other side, in the opposite direction. If the propagation of the depolarization wave in the opposite direction *is slow enough*, it will find a healthy myocardium capable of depolarizing again after leaving the site of the blockage. Then a premature impulse occurs, i.e. extrasystole. The whole cycle is then repeated, in order to create a new extrasystole, that is, tachycardia is established. Such a mechanism of arrhythmia is called "re-entry phenomenon" (English: " 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, mostly by blocking them. As antiarrhythmics primarily bind to the channels that open more often, 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.

In **the first group** there are drugs that block sodium ion channels and thus make depolarization more difficult (they are said to "stabilize" the membrane). Although they act on N a $^{+}$ channels in all parts of the heart, they significantly block the channels in the parts of the heart that depolarize more often and more easily - and these are precisely the parts of the heart affected by the pathological process (this is the so-called use-dependent blockade - English: " use - dependent blockade ") and parts of the conducting system (His bundle and Purki - her fibers). Depending on how they affect the length of the action potential, they are divided into 3 subgroups:

- Ia - medicines which one extend action potential and re fractional period (in to whom se cells not I can again de polarisati) - quinidine , procain - amide , disopyramide and moricizine . They they slow down phase 0, slow down spon tanu depolarization in phase 4 i they slow down implementation in to the heart .
- And b - medicines which one shorten action potential and refract terni period - lidocaine, mexiletine , tocainide and Fe Nitoin .
- And c - medicines which one not affect on the length action potency _ and refractory period - encainide, flecainide and propafenone .

Medicines from the Ia group are very effective, but have a lot of unwanted effects. All have a negative inotropic effect and all can cause arrhythmias if inadequately dosed. Quinidine has pronounced central side effects (ringing in the ears, dizziness and a state similar to drunkenness), has a toxic effect on the bone marrow and can cause a characteristic ventricular tachycardia that looks like a series of spikes in the EKG - French: " torsades " de pointes "). Procaine-amide in people who slowly break down this drug (so-called slow acetylators) can cause a syndrome similar to systemic lupus erythematodes. Disopyramide has pronounced antimuscarinic side effects (dry mouth, constipation, urine retention, etc.).

Quinidine is an alkaloid from plants of the Cinchona species (China-tree), which grow 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 the contractions of the pregnant uterus, and exhibits an anticholinergic effect. In the EC G of a patient receiving quinidine, prolongation of the PR, QRS and QT intervals can be seen. Due to negative inotropic and vasodilatory 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 previously received digoxin, which controls the number of impulses that pass from the atria to the ventricles through the AV node ; due to its anticholinergic effect, quinidine could increase the permeability of the AV node and lead to dangerous ventricular tachycardia), to *maintain sinus rhythm* after electro-conversion of atrial fibrillation or flutter to sinus rhythm, to *interrupt ventricular tachycardia* and to suppress *tachycardia attacks* in Wolff-Parkinson - White's 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 a block of impulse conduction or provoke the appearance of ventricular arrhythmias. Thrombocytopenia may occur in a small number of patients. Large doses of quinidine can lead to the appearance of "cinchonism" syndrome, which consists of the following symptoms: ringing in the ears, headache, nausea, blurred vision, dizziness, confusion. Extremely large doses of quinidine lead the patient into delirium with hallucinations.

Quinidine increases the concentration of digoxin in the serum, so the dose of digoxin must be reduced in order 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 being antiarrhythmic, has a negative inotropic and hypotensive effect. Because of its short duration of action that requires frequent administration of the drug, procainamide is used in patients who cannot tolerate or have not responded well to quinidine.

Adverse effects of procainamide include conduction block in the heart, ventricular arrhythmias, confusional state (rare), agranulocytosis (rare) and **syndrome similar to systemic lupus** (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 (rare).

Moricizine exhibits effects on the myocardium that are common to groups I a and I b. 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, because it increases mortality.

Drugs from group I b are the safest to use than antiarrhythmics of the first group (they do not have a negative inotropic effect on the myocardium), but if they are overdosed, they can cause excitation of the central nervous system (confusion, convulsions) and arrhythmias.

Lidocaine, by blocking 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. In EK G , a shortening of the QT interval can be observed . Lidocaine is indicated for the suppression of ventricular arrhythmias in patients with myocardial infarction, as well as for the treatment of arrhythmias in case of intoxication with cardiotonic glycosides.

Due to 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 quickly broken down in the liver.

Lidocaine causes drowsiness in most patients, while some experience paresthesias, disorientation, psychosis, and convulsions. It rarely causes hypotension in 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 for the treatment of ventricular arrhythmias after myocardial infarction, anesthesia, cardiac catheterization, and with the simultaneous use of cardiotonic glycosides (here it is particularly effective, because it removes the depressing effect of digoxin on conduction in the AV node). It should not be given to patients with atrial fibrillation or flutter, because it can accelerate the conduction of impulses into the ventricles.

Tocainide has a similar chemical structure to lidocaine. Its effects on the myocardium are similar to those of lidocaine. It is used orally in the treatment of symptomatic ventricular arrhythmias, which have not responded to other antiarrhythmics.

In about 15% of patients, the drug causes dizziness or nausea. Paresthesias and tremors also occur relatively often. Very rarely, serious side effects may occur, such as thrombocytopenia, agranulocytosis or pulmonary fibrosis.

Mexiletine acts very similarly to lidocaine and tocainide. It is administered orally for the treatment of ventricular arrhythmias. It has a beneficial effect on people with congenital prolongation of the QT interval. Adverse effects of mexiletine are: hypotension, dyspepsia, tremor, dizziness and coordination disorder.

Medicines from the I c group are rarely used today, because in a small (but significant) number of patients they cause the appearance of fatal arrhythmias.

Flecainide blocks sodium channels and slows conduction in all parts of the heart, especially in the bundle of His and Purkinje fibers. In EC G, prolongation of PR interval, QRS complex and QT interval can be seen. 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.

Adverse effects of flecainide are: dizziness, visual disturbances, headache, worsening of heart failure and occurrence of 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 the refractory period, and in the AV node and ventricles it only slows down the conduction. It also slows down the work of the sinus node. In EK G, prolongation of PR interval and QRS complex can be seen. 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-arrhythmogenic effect.

In one third of patients, propafenone causes nausea and dizziness.

In the II group of antiarrhythmics there are beta-blockers (pro - pranolol, acebutolol, esmolol, etc.) that reduce the arrhythmogenic effect of the sympathetic nervous system on the heart.

In addition to beta-receptor blockade, propranolol acts directly on the myocardium, similar to quinidine. It slows down the work of the sinus node and conduction in the AV node, atria and ventricles. In EC G, a prolongation of the PR interval can be seen. Propranolol is used for the treatment of atrial and ventricular arrhythmias that are the result of excessive sympathetic activation (after myocardial infarction, when using general anesthetics, etc.). Along with digoxin or alone, propranolol is also used to control ventricular rate in patients with atrial flutter or fibrillation. It is also the drug of choice for patients with congenital QT prolongation.

Esmolol is a selective beta1-blocker, which only works for about 20 minutes, due to its rapid breakdown in the plasma, under the action of the esterase enzyme. It is administered intravenously for rapid control of the frequency of the ventricles in patients with atrial flutter or fibrillation.

Group III includes drugs that prolong the action potential and the refractory period, most likely by blocking channels for K^+. These are bretylium, sotalol, dofetilide and ibutilide. Sotalol also blocks beta-receptors. By extending the action potential, the refractory period is also extended, so that *re - entry* termination mechanism. Medicines from this group, like all other antiarrhythmics, can sometimes cause arrhythmias themselves.

Bretylium is a very effective antiarrhythmic, which 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 blockade of adrenergic neurons. It causes more pain, vomiting and swelling of the parotid glands.

Besides the direct effect on the myocardium, Sotalol blocks beta-receptors. It extends action potential duration and refractory period. It reduces the systolic pressure and stroke volume of the heart. It is used for the treatment of both ventricular and atrial arrhythmias. Sotalol is administered orally.

Sotalol may cause ventricular arrhythmias, especially in individuals with prolonged QT interval. It can also cause side effects characteristic of beta-blockers.

Dofetilide selectively inhibits the fast component of the outward 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. In EC G, prolongation of the QT interval can be observed. 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 ventricular arrhythmia " torsades" 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.

Very similar to dofetilide is **ibutilide**. The only difference is that it breaks down quickly in the liver, so it must be administered parenterally. It is used to chemically convert atrial fibrillation and flutter to sinus rhythm.

In group IV antiarrhythmics are calcium channel blockers (verapamil and diltiazem). **Verapamil** blocks the entry of calcium ions through L -type channels into cardiac myocytes. Thus, it slows down the spontaneous depolarization of S A-node cells and slows conduction through the AV -node. Verapamil is used to treat atrial arrhythmias and to slow 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 from the body very slowly ($t_{1/2} \approx 100$ days). It is metabolized in the liver to active metabolites, which are excreted in the bile. It works in several ways: blocking Na^+ and K^+ channels, blocking beta-receptors and blocking calcium channels. It prolongs the action potential and the 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 torsade-type ventricular arrhythmia. It is used for all types of arrhythmias, especially for the most severe ventricular arrhythmias. Unfortunately, the drug has pronounced toxicity outside the heart. It can cause hypothyroidism (due to the iodine it contains), corneal clouding, dark skin discoloration, hair loss, photosensitivity, tremors, nightmares, peripheral neuropathy, pulmonary fibrosis, and liver damage.

The 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, blocking beta-receptors and blocking calcium channels. Dronedarone must not be given to people who have or have had heart failure, because it can worsen or provoke it. It is less toxic than amiodarone, but may still cause pulmonary fibrosis in a minority of patients.

Adenosine also occupies a special place among antiarrhythmics. Acting on its receptors, which are found only in the atria and AV node, adenosine opens channels for potassium and thereby reduces the rate of spontaneous depolarization. In the AV node, adenosine slows conduction. As an intravenous bolus injection, adenosine interrupts atrial and nodal (from the AV node) tachycardia. Its effect lasts only 15 seconds, because it is quickly broken down in erythrocytes.

Adenosine causes a brief rise in blood pressure, followed by hypotension. Facial flushing and bronchospasm occur. It should not be given to people who have 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

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Procainamide	orally	500 mg	4 hours
Quinidine	orally	200 mg	6 o'clock
Lidocaine	and . c .	50 mg as a bolus and . c . injections, then 20 μg / kg / min in and . c . infusion	
Mexiletine	orally	300 mg	8 hours
Amiodarone	orally	600 mg	24 hours
Propranolol	orally	20 mg	6 o'clock
Bretylium	and . c .	5 mg /kg bolus	1 mg/min i.v. infusion
Verapamil	and . c .	0.1 mg / kg	After 30 min. repeat as necessary

TREATMENT OF ARRHYTHMIAS

Extrasystoles are treated only if there is morphological damage to the myocardium; then it is best to use β-blockers.

Paroxysmal supraventricular tachycardia can be suppressed by stimulation of the vagus (eg Valsalva maneuver). If this fails, the i.v. by applying vera-pamil; it is especially indicated in patients without myocardial or valvular disease. Another possibility is the intravenous administration of adenosine. Adenosine has an advantage over verapamil in that it can also be used in situations where the patient has previously received ββ-blockers.

Atrial fibrillation and flutter. While in flutter the therapeutic goal is to restore sinus rhythm, in fibrillation the aim is only to control the number of impulses that pass into the ventricles per unit of time.

Flutter can be converted to sinus rhythm by electroshock or the use of amiodarone or dofetilide. In both cases, a few months before conversion, the patient should undergo anticoagulant therapy, in order to prevent the possibility of embolism.

The frequency of heart chambers in atrial fibrillation can be controlled βwith a -blocker or verapamil in people without heart failure, while the use of digoxin is more cost-effective in people with heart failure. In elderly people with atrial fibrillation, or in those with valvular or myocardial diseases, the use of oral anticoagulants is indicated, in order to prevent the formation of thrombus in the atria, and then embolism.

Ventricular tachycardia is treated acutely with lidocaine, and when the condition stabilizes, other antiarrhythmics of group I or amiodarone are used.

Torsade ventricular tachycardia is a special entity *de pointes*, which is caused by drugs that prolong the QT interval. This arrhythmia is terminated by intravenous administration of magnesium sulfate (8 mmol M g $^{2+}$ over 10-15 minutes).

DRUGS AGAINST HYPERLIPIDEMIA

After the absorption of triglycerides and cholesterol from food, chylomicrons are formed in the epithelial cells of the small intestine - complex particles whose center consists of triglycerides and cholesterol, and whose surface consists of phospholipids and proteins. Chylomicrons reach the venous blood through lymph flow, and then reach the peripheral tissues (fat and muscle), where they are broken down by the enzyme lipo-protein 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) which contain a lot of cholesterol. Normally, LDLs bind to their receptors on hepatocytes and are taken up by liver cells. In the case of excess LDL (e.g. with an overabundant diet full of cholesterol), they are taken over by the cells of the intima of the blood vessels. Excessive accumulation of LDL in these cells leads to their transformation into foam cells and, finally, to death and plaque formation. In the period between meals, the liver creates VLDL (very low density lipoproteins), which contain triglycerides and cholesterol. VLDL go to peripheral tissues, which, after degradation under the action of lipoprotein lipase, supply fatty acids and glycerol. The rest of VLDL is converted into LDL via IDL.

Hyperlipidemias can be congenital or acquired. Congenital hyperlipidemias may predominantly have elevated cholesterol or triglycerides. Normally, the level of triglycerides in the serum should be less than 2.5 m M/ l, and the cholesterol level should be below 4.4 m M/ l.

The first step in treating hyperlipidemia is diet. The patient must reduce fat intake below 20% of the total caloric value of the meal, and cholesterol in particular below 200 mg /day. After 3 months, the diet should again measure the concentration of lipoproteins (or at least triglycerides and cholesterol) and if they are elevated, drug therapy should be applied.

Hypertriglyceridemia (hyperlipidemia dominated by an increase in triglycerides) is treated ***with fibric acid derivatives*** (fenofibrate, gemfibrozil, clofibrate). These drugs activate a nuclear receptor called "peroxisome proliferator-activated receptor" (PPAR), which increases the transcription of the gene for lipoprotein lipase, and decreases the transcription of the gene for apolipoprotein C 3 (which normally 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 A $_1$.

Fibrates are used to treat congenital hyperlipidemias in which triglycerides are elevated: familial hypertriglyceridemia (type 4) and dysbetalipoproteinemia (type 3). In case of dysbetalipoproteinemia, fibrates must be used together with a drug that lowers cholesterol, e.g. with nicotinic acid. Also, fibrates have a beneficial effect on secondary hyperlipidemia, which occurs in patients with type 2 diabetes.

Unfortunately, fibric acid derivatives have a lot of serious side effects that limit their use (more frequent gall bladder calculus, myositis, hepatitis, erectile dysfunction, nausea). In addition, they increase the concentration of LDL, lipoproteins that promote the development of atherosclerosis.

Fibrates should not be given together with statins, because the risk of myositis increases. Also, fibrates potentiate the anticoagulant effect of warfarin.

An alternative drug for the treatment of hypertriglyceridemia is ***nicotinic acid*** (niacin). It reduces the formation 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 this leads to a decrease in triglycerides and cholesterol in the blood. It also increases the level of HDL particles in the plasma. That is why nicotinic acid, in addition to the treatment of hypertriglyceridemia, is also used for the treatment of hypercholesterolemia. It is used independently for the treatment of hypertriglyceridemia type 4, in combination with statins for the treatment of hyperlipidemia type 2b, and in combination with fibrates for the treatment of dysbetalipoproteinemia (type 3).

Nicotinic acid leads to the release of prostaglandin and a flu-like syndrome. By taking aspirin 30 tablets ’before nicotinic acid, and taking the medicine with food, this syndrome can be prevented. After prolonged use, hepatitis, hyperglycemia and hyperuricemia occur.

Hypercholesterolemia can also be treated with ***anion exchange resins*** (cholestyramine or cholestipol), which are taken orally, are not absorbed in the digestive tract, and bind (ionic bonds) bile acids. This increases the excretion of bile acids through feces, and reduces the amount of bile acids that after reabsorption in the ileum reaches the liver again. In the liver, the production of bile acids from cholesterol intensifies, so LDL particles are taken up more from the blood because the number of receptors for LDL on hepatocytes increases. Considering that they are not absorbed, these preparations, except for bloating and sometimes constipation, have no significant side effects. Only in smaller children, due to the release of chlorine ions from the resins due to the binding of bile salts, hyperchloremic acidosis can occur. Since they are taken in larger quantities (about 20 grams per day), and they have an unpleasant taste, they are usually used mixed with fruit juice.

The 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, and thus interfere with their absorption. That is why other medicines are not applied one hour before, and 4-6 hours after taking resins.

A new group of drugs, very effective in the treatment of hypercholesterolemia, consists of ***hydroxymethyl-glutaryl-SoA reductase inhibitors*** (HMG -reductase, an enzyme that catalyzes the key reaction in cholesterol synthesis, converting hydroxymethyl-glutaryl into mevalonate). They reduce the synthesis of cholesterol in the liver, so LDL particles from the blood are taken up by the liver more, due to the increased number of LDL receptors on the hepatocytes. Lovastatin, simvastatin, atorvastatin, fluvastatin and others from this group (we call them *statins under one name*) significantly lower the level of cholesterol and LDL in the circulation.

In addition to the mentioned 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 for the treatment of 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 their cholesterol level, because they have been shown to reduce the frequency of repeated infarctions. Such application is called secondary prevention.

The problem in their application is unwanted effects: rare but serious rhabdomyolysis and chemical hepatitis. The patient should be warned to contact the doctor at the first appearance of muscle pain, in order to prevent the development of extensive rhabdo-myolysis, with the release of myoglobin and blockage of the renal tubules (ie, with the development of acute renal failure). The simultaneous use of statins and fibric acid derivatives should be avoided, as the risk of rhabdomyolysis increases.

Lovastatin, simvastatin and atorvastatin are metabolized in the liver via cytochrome P 450 3A4, and fluvastatin via isoform 2 C 9. Medicines and foods that inhibit cytochrome 3A4 slow down the metabolism of statins and increase their concentration in the blood 8-10 times. These are: itraconazole, erythromycin, ciclosporin and grapefruit juice. Conversely, drugs that stimulate the activity of cytochrome 3A4 (phenobarbitone, carbamazepine, rifampicin) accelerate the metabolism of statins and lower their concentration in the blood. Since warfarin, like fluvastatin, is metabolized via cytochrome 2 C 9, the two drugs interfere with each other's elimination and increase blood concentrations.

A few years ago, an even more effective drug for lowering blood cholesterol levels was discovered - 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 degradation of the LDL receptor . The consequence is an increase in the number of receptors and a greater uptake of cholesterol from the bloodstream, i.e. a drop in cholesterol levels in the blood . Evolocumab is applied subcutaneously, once a month, and reduces the level of cholesterol in the blood by as much as 75% (the maximum effect of statins is about 45%) . The main side effects of evolocumab are arthralgia and increased frequency of various infections.

A special group of drugs is represented by substances that prevent fat absorption. The first drug to emerge from this group was **orlistat,** a pancreatic lipase inhibitor. 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 effectiveness in the treatment of obesity (the annual weight loss is 4 kg greater with the use of both orlistat and diet than with diet alone), it has no clinically significant effect on serum cholesterol and triglyceride levels.

Ezetimibe is the drug that recently came into use. It selectively inhibits the absorption of cholesterol as well as it inhibits the similar phytosterols. It successfully reduces the level of cholesterol, LDL lipoprotein and apolipoprotein B in patients with primary hypercholesterolemia. It is always used in combination with HMG -SoA reductase inhibitors. The drug is administered once a day, orally, in 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 transport 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 that after the administration of this drug, the secretion of chylomicrons from the intestines and VLDL lipoproteins from the liver into the bloodstream decreases. Lomitapide reduces the level of cholesterol and triglycerides in the blood by about 40%. The medicine is taken orally. It is perfectly absorbed from the intestine, but it is metabolized in the liver to cytochrome P 450 3A4 already during the first passage, so its bioavailability after oral administration is only 7%. It is liposoluble and penetrates all tissues. May increase serum aminotransferase levels.

Mipomersen is an antisense oligonucleotide (20 nucleic bases) that binds ***to transport RNA*** encoding apolipoprotein B. The resulting complex is broken down by one RN K-ase, so that less apolipoprotein B is created, and thus less chylomicrons and VLDL are secreted 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 the level of triglycerides and cholesterol by about 30%. Among the side effects, it causes a flu-like condition after the injection, and can increase the level of aminotransferases in the serum.

Table 16. Doses of hypolipemic agents

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Nicotinic acid	orally	500 mg	8 hours
Gemfibrozil	orally	600 mg	12 o'clock

Atorvastatin	orally	20 mg	12 o'clock

PHARMACOLOGY OF HORMONES

HORMONES OF THE HYPOTHALAMUS AND PITUITARY

The hypothalamus secretes substances that control the release of hormones from the anterior lobe of the pituitary gland.

A polypeptide of 10 amino acids that is secreted in the hypothalamus through the portal system reaches the pituitary gland and there leads to the release of gonadotropic hormones, follicle-stimulating (FSH) and luteinizing (LH). This polypeptide is called **gonadotropin-releasing hormone (GRH)**. GRH is used to induce ovulation in people suffering from sterility. In order to achieve this effect, it is necessary to administer GRH 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 analogues of GRH (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. That is why GRH analogs are used for the treatment of cancers dependent on sex hormones (prostate cancer, breast cancer and others), endometriosis, hirsutism and other diseases where it is desirable to reduce the release of FSH and LH. Analogues of GRH are applied parenterally, in the form of subcutaneous injection, because they are also peptides according to their chemical composition. Hot flashes, erectile dysfunction and loss of libido occur in patients after the use of GRH analogues.

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 **human chorionic gonadotropin** (a hormone of the corpus luteum and placenta that is produced in large quantities is used instead and found in the urine of pregnant women hHG), which has very similar effects. Both preparations are used sequentially to induce ovulation in patients suffering from sterility and to stimulate spermatogenesis in men. Human chorionic gonadotropin can sometimes cause a testicle that is left behind in the inguinal canal to descend (undescended testicle). Recently, human follicle-stimulating hormone (**rFSH**) has been synthesized by recombinant technique, which is the same or somewhat more effective than human menopausal gonadotropin, so it can be used instead. Also recently, recombinant human luteinizing hormone (**r - hLH**) has been successfully used instead of human chorionic gonadotropin.

Somatostatin is a hypothalamic polypeptide of 14 amino acids that reduces the secretion of pituitary somatotropic 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 analogue of 8 amino acids - **octreotide -** is more often used, which is more effective and whose effect lasts longer. Octreotide is successfully used in the treatment of carcinoid syndrome, gastrinoma, glucagonoma and watery diarrhea syndrome, hypokalemia and achlorhydria. An adverse effect of this drug is the appearance of biliary calculosis due to inhibition of gallbladder motility. Apart from 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 somatotropic hormone in the pituitary gland. It is used to treat acromegaly, neuroendocrine tumors and thyrotropic adenomas.

Somatotropic hormone is used to achieve normal height in persons with dwarfism due to insufficiency of the anterior lobe of the pituitary gland. In the past, STH was obtained by extraction from the pituitary glands of deceased persons; however, since more cases have been identified **Creutzfeld-Jakobov** disease (spon-giosis degeneration of the central nervous system) due to the transmission of one type of protein (the so-called prion protein), this hormone is no longer obtained in the mentioned way. Today, an analogue of the STH hormone, **soma-tropin**, obtained by recombinant means is used. Growth hormone (somatotropic hormone) is also successfully used to treat ***cachexia*** in people with chronic diseases or acquired immunodeficiency syndrome.

Pegvisomant is a somatotropic hormone receptor blocker, which is chemically a protein. It is administered as a subcutaneous injection to treat 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 application in dwarfism therapy is still in the experimental phase. Its other name is **somato-relin**, and for now it is used only in diagnostics.

The hypothalamic tripeptide called thyrotropin-releasing hormone (**TRH) increases the secretion of pituitary thyrotropin hormone**. It is used only in the diagnosis of thyroid gland disease. Thyrotropin (TSH) is used in the treatment of thyroid cancer. Administered simultaneously with radioactive iodine (^{131}J), TSH increases its entry into tumor cells and thus enhances the tumoricidal effect.

The secretion of prolactin in the anterior lobe of the pituitary gland is reduced by dopamine from the hypothalamus. Increased prolactin secretion (eg in pituitary adenomas) results in gynecomastia and impotence in men, and galactorrhea and amenorrhea in women. It can be suppressed with a dopamine analog, one of the alkaloids of ryegrass - **bromocriptine**. In addition, bromocriptine is used to stop normal breastfeeding when necessary (for example in breast abscess) and to treat acromegaly (because it reduces the

release of STH from pituitary tumors). The dose of bromocriptine to stop lactation is 2.5 mg twice a day for two weeks. As a dopamine analogue, bromocriptine is also a useful drug for the treatment of parkinsonism (see the chapter on parkinsonism). Side effects of bromocriptine are: dystonia (involuntary movements), confusional state with hallucinations, hypersexuality and hypotension. In addition to bromocriptine, other agonists of dopamine receptors - **cabergoline - can be used to suppress hyperprolatinemia**. The effectiveness of cabergoline is similar to the effectiveness of bromocriptine, but its effect is much longer, so it is usually used only in one dose to stop lactation.

Adrenocorticotropic hormone (ACTH) is also secreted in the anterior lobe of the pituitary gland. **ACTH** controls the secretion of steroid hormones in the adrenal cortex. It is used exclusively in the diagnosis of adrenal diseases. ACTH secretion 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 the last one lobe pituitary gland

Neurons from the paraventricular and supraoptic nuclei of the hypothalamus send their axons to the posterior lobe of the pituitary gland. Two hormones are secreted at the ends of these axons: oxytocin and vasopressin (antidiuretic hormone). Both hormones are octapeptides.

Oxytocin causes contraction of the pregnant uterus: its increased release leads to childbirth. It also contracts the myoepithelial cells around the acini of the mammary gland and leads to secretion of milk during breastfeeding. It is used for the induction (starting) of labor in prolonged pregnancy and for the stimulation of uterine contractions during labor that lasts too long. It is then given i.v. infusion (5 I J of oxytocin in 500 ml of 5% glucose is brought in, so initially the infusion rate is 8 drops/min; the rate then gradually increases to a maximum of 40 drops/min). In the form of a nasal spray, oxytocin can be used in nursing mothers with milk retention for better breast emptying.

Recently, there is more and more evidence that oxytocin promotes 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) at physiological concentrations increases the reabsorption of water from the collecting ducts of the kidney (by causing the incorporation of water channels into the luminal membrane of the collecting duct cells). In about 100 times higher concentrations, it contracts 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 ($t_{1/2}$ 10 minutes), the analog ≈**desmopressin** (1-desamino-8- D -arginine vasopressin) is used for the treatment of diabetes insipidus, which breaks down more slowly ($t_{1/2}$ ≈75 minutes), so it can be applied sublingually only twice a day.

Recently, the administration of vasopressin with adrenaline in patients with cardiac arrest has been shown to reduce brain damage after resuscitation. This opens the possibility for vasopressin to become a routine therapy for cardiac arrest.

ATOSIBAN

Atosiban is an oxytocin receptor blocker with a tocolytic effect, i.e. it relaxes the uterus, which contracts during labor earlier or more than physiologically. Its effectiveness in suppressing premature contractions and preventing premature birth is the same as the effectiveness of β_{2-} agonists or calcium channel blockers (primarily nifedipine), but it has one advantage: it exhibits fewer cardiovascular and neurological side effects than β_2 -agonists (tachycardia, hypotension, tremor) and calcium channel blockers (redness, palpitations, hypotension).

The indication for the use of atosiban is the prevention of uncomplicated preterm birth between the 24th and 33rd weeks of gestation. It is especially indicated for pregnant women who have heart disease at the same time.

Atosiban is administered as an 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.

As already mentioned, in addition to atosiban, beta 2 agonists can be used intravenously (ritodrine, hexoprenaline, fenoterol) or calcium channel blockers (primarily nifedipine) orally to prevent premature birth. In both cases, the application of therapy is limited to a few days. Beta 2 agonists have the most side effects when used in this indication (prevention of premature birth).

DRUGS AGAINST DIABETES

Diabetes mellitus is a disease that is a consequence of insulin deficiency (hormone β- pancreatic cells) and/or reduced sensitivity of peripheral tissues to insulin. It occurs in two forms: insulin-dependent diabetes (IZD or type 1) and insulin-independent diabetes (IND or type 2). IZD usually begins in childhood or early youth due to autoimmune damage βto the cells of the pancreas, and IND in

later life due to exhaustion βof the cells through continuous hyperstimulation (due to excessive nutrition). In IZD, insulin practically does not exist in the blood, while the level of glucagon is elevated. In IND, the level of insulin in the blood is usually sufficient to prevent the onset of ketoacidosis, and the reduced sensitivity of peripheral tissues to insulin and the reduced response of pancreatic beta cells to glucose from the blood dominate. In principle, IZD is treated with insulin, and IND with oral hypoglycemic drugs and/or insulin. Insulin is a peptide hormone (51 amino acids) consisting of two chains connected by disulfide bonds.

It is produced by the hydrolysis of proinsulin, a long protein chain, in Golgi cisternae. From the prionsulin becoming insulin and C - peptide , which does not have none function . Insulin is then deposited in the beta cell granules, where it forms crystals made up of six insulin molecules and two zinc atoms. Insulin activity 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. Precisely measurements is shown yes 1 mg insulin has activity from the around 28 I J . The whole human pancreas _ in there were com moment contents _ _ about 200 I J insulin .

Insulin is degraded in the liver and kidneys by hydrolysis of disulfide bridges. The half-elimination time of insulin is 4-5 minutes.

Insulin promotes the entry of glucose and amino acids into cells (by leading to the appearance of transporters on the outer membrane), inhibits gluconeogenesis and promotes glycolysis. Increases protein and fat synthesis 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 technique (the gene for insulin is inserted into microorganisms that then synthesize insulin). Compared to natural insulin, it differs in that two amino acids have changed places: proline from position B 28 and lysine from position B 29. It is applied subcutaneously, after 1 hour it reaches the maximum concentration in the blood, and it works for 3-4 hours. Two more insulin analogs have an ultrashort action: **insulin aspart and insulin glulisine**. Ultra-short-acting insulins are suitable for administration before meals, because the patient can practically start eating immediately.

Ordinary, natural insulin (popularly called "crystal") acts for a short time (its effect starts in 30 minutes, reaches its 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 which after s . c . applications gradually release insulin and thus have a medium-long or long-acting effect. In recent years, the use of protamine has been avoided. Medium-long-acting **insulin lente** (a mixture of 30% insulin semilente and 70% insulin ultralente; insulin semilente - an amorphous form of insulin (does not crystallize) that acts for a short time, but is no longer used continuously) and isophane **insulin** (a mixture of insulin and protamine). Their effect starts in about 2 hours and lasts up to 24 hours.

Long-acting insulin **ultralentes and protamine-zinc-insulin,** in which even larger amounts of zinc or protamine have been added. Their effect starts in 4 hours and lasts up to 36 hours. All preparations, except the crystalline one, can only be applied subcutaneously. The new long-acting insulin preparation is ***glargine***. It contains two molecules of arginine more than natural insulin at the COOH -end of the B chain, and instead of asparagine at position A21 it has glycine. Glargine has an advantage over other preparations in that it provides an even level of insulin for more than 24 hours (without peaks). Another insulin analog, ***insulin detemir***, which has a saturated fatty acid added to the amino group of lysine 29, behaves similarly. The newest long-acting insulin analog is ***insulin degludec***, which causes hypoglycemia less often than insulin ultralente or protamine-zinc-insulin.

Usually animal-derived insulin preparations contain a mixture of two types of insulin (eg, bovine insulin and porcine insulin); sometimes, however, the preparation is prepared from only one type of insulin (eg, only from beef or pork). We call such insulins "monocomponent" and use them in case of the appearance of antibodies to insulin of one animal species. Increasingly, instead of insulin of animal origin, insulin of human origin is used. They are less immunogenic, so resistance to them develops more slowly.

The classic regimen of insulin administration involves the administration of a fixed daily dose of medium- or long-acting insulin that ensures the basal level of the hormone, and the additional administration of short- or ultra-short-acting insulin before each meal. For ease of application, the so-called mixed preparations, which contain intermediate-acting insulin (usually isophane insulin) and insulin lispro, and which can be administered once or twice a day.

Intensive treatment with continuous infusion of natural insulin should be applied to patients who cannot achieve glycemic control with the usual dosing regimen. 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 does intensive therapy with precise glycemic control. Insulin-dependent diabetes is always treated with insulin. Patients with insulin-independent diabetes switch 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.

Adverse effects of insulin are:

a) **hypoglycemia** (glucose in plasma below 2.5 mmol / l) - occurs if insulin is overdosed or is not accompanied by adequate nutrition. 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. administration of 50 ml of 50% glucose (after the injection,

it is mandatory to inject a saline solution to wash out the vein, otherwise thrombophlebitis will occur), glucagon (1 mg s.c.) or, if the patient is conscious and in the early phase of hypoglycemia, oral administration of glucose

b) **atrophy of fatty tissue** at the site of . c . injection (avoided by frequent change of application site)

c) **resistance** to insulin due to the formation of antibodies (antibodies are formed even to human insulins!)

d) insulin allergy of the first or third type.

Oral hypoglycemics are used only in IND therapy. There are several groups of oral hypoglycemics according to their chemical structure and mechanism of action: sulfonylurea derivatives, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase blockers, incretin analogs, 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 βcell membrane, cause membrane depolarization, entry of Sa^{++} ions and release of insulin. Calcium causes the contraction of myosin fibrils, which lead to the exocytosis of insulin granules and the release of insulin. In addition to increasing insulin secretion, these preparations decrease glucagon secretion, which contributes to the control of hyperglycemia. Among the preparations from this group, there is no significant difference in efficiency, only the preparations from the second generation have slightly fewer side effects. Problems in their application are the possibility of hypoglycemia, intolerance to alcohol (due to an effect similar to disulfiram /chlorpropamide), 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 as sulfonylurea derivatives, i.e. increase insulin release from beta cells. They work quickly and for a short time (up to 2-3 hours), so they are used to control postprandial spikes in glycemia (taken immediately before a meal).

Biguanides (metformin) promote the entry of glucose into the cells of peripheral tissues and reduce the production of glucose in the liver, so they are also effective in patients who no longer have functional βpancreas cells. They also reduce glucagon levels. They almost never cause hypoglycemia, so they are called "euglycemic" drugs. The downsides are their tendency to cause lactic acidosis, metallic taste and loss of appetite. Metformin is well absorbed and excreted unchanged in the urine. It has a short half-elimination time of 2-3 hours.

Metformin is mostly 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 IND who do not respond to diet or diet and the aforementioned hypoglycemic agents, 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 epithelium of the small intestine. Inhibition of these enzymes hinders the digestion of disaccharides (sucrose, maltose) and thereby slows down and reduces the absorption of glucose. In previous clinical studies, it has been shown that acarbose reduces the concentration of glycosylated hemoglobin in patients, but it is not yet clear whether this drug can slow down 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 cannot cause hypoglycemia.

Thiazolidinediones are new drugs (rosiglitazone and pio-glitazone) 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 redistribution of fat: visceral fat tissue decreases and peripheral fat tissue increases.

Rosiglitazone and pioglitazone rarely lead to hypoglycaemia. They reduce the level of triglycerides and increase the level of HDL and LDL lipoproteins. 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 doctors who prescribe it are advised to strictly monitor patients for early signs of heart failure. Other side effects are mild anemia, edema and induction of cytochrome P 450 in the liver, which reduces the effects of other drugs (eg oral contraceptives). Clinically, pioglitazone is used to treat insulin-independent 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 task is to facilitate the absorption and utilization of nutrients, especially glucose. The two most important incretins are ***glucagon-like peptide 1*** (PNG 1) and ***insulinotropic glucose-dependent polypeptide 1*** (IPZG 1). It has been observed that in type 2 diabetes the secretion of PNG 1 decreases, and that the addition of this hormone improves glycemic control in patients with this disease.

Recently, drugs that supplement or enhance the effect of endogenous incretins have been introduced into clinical practice. **Exenatide and liraglutide are** PNG 1 receptor agonists. Exenatide was isolated from the saliva of the venomous Gila Monster lizard. Both drugs are administered by subcutaneous injection. Like PNG 1, exenatide and liraglutide prevent glucagon secretion, slow down

gastric emptying, increase insulin secretion and reduce appetite through central action. All these effects ultimately lead to the normalization of blood glucose levels. It is used as an additional therapy in patients who cannot achieve glycemic control using two oral antidiabetics (one sulfonylurea derivative plus one biguanide). The main side effects are hypoglycemia, gastrointestinal complaints and the formation of antibodies to exenatide and liraglutide. **Saxagliptin, vildagliptin and sitagliptin** inhibit dipeptidyl-peptidase 4, resulting in a decrease in the breakdown of **incretins** (glucagon-like peptide 1 and gastric inhibitory polypeptide) that accumulate and lead to increased insulin secretion, decreased glucagon secretion and slower gastric emptying. They are used in type 2 diabetes alone or in combination with other oral antidiabetics, in a situation where other antidiabetics 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, which brings glucose into the striated muscle cells, increases, and gluconeogenesis in the liver decreases. This group includes ***dapagliflozin and canagliflozin***. These drugs can be combined with other antidiabetic drugs. They increase the frequency of infections of the urogenital tract and lead to hypotension; rarely cause hypoglycemia.

The newest group of antidiabetics (which is still under investigation) consists of ***glitazars***: muraglitazar and tesaglitazar. Glitazars also activate PPARs alpha and PPAR gamma, leading simultaneously to lower triglycerides and lower glycemia, two disorders that often coexist in patients with type 2 diabetes. Muraglitazar and tesaglitazar have not yet been approved for widespread use because they have been shown in clinical studies to increase the risk of heart attack. insufficiency and transient ischemic attacks.

Amylin

Amylin is a hormone that is secreted together with insulin from the beta-cells of the islets of Langerhans. It reduces the release of glucagon, slows down the emptying of the stomach and, through its central action, reduces the feeling of hunger. **Pramlintide**, a synthetic analog of amylin, is administered subcutaneously, immediately before a meal, in patients with type 1 and 2 diabetes. It helps regulate glycemia in patients who do not respond to conventional therapy.

The main side effects of pramlintide are hypoglycemia and gastrointestinal disturbances.

Glucagon

Glucagon is a peptide hormone secreted by α-cells of the pancreas. It causes glycogenolysis and the release of glucose from the liver; it also increases the force of heart contraction.

Glucagon is used to treat hypoglycemic coma and acute heart failure. It is administered parenterally (i.v. , i.m. or s.c.) in a dose of 1 mg .

The use of glucagon is contraindicated in patients with pheochromocytoma, because it leads to the sudden release of a large amount of catecholamines from the tumor.

Drugs that reduce the incidence of microangiopathy as a complication of diabetes (and consequent retinopathy, nephropathy, neuropathy, diabetic foot)

Today, it is considered that microangiopathy as a complication of diabetes occurs due to the creation of free oxygen radicals and the accumulation of sorbitol in endothelial cells. That is why **antioxidants** (primarily alpha-lipoic acid) and **inhibitors of aldose reductase**, the enzyme that reduces glucose to sorbitol, are used in the prevention of microangiopathy in diabetics. Of the aldose reductase inhibitors, ***epalrestat*** entered clinical use. While alpha-lipoic acid only somewhat reduces the symptoms of neuropathy, 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 side effects have been reported in clinical studies to date.

THYROID HORMONES AND ANTITHYROID DRUGS

The synthesis of thyroid hormones (triiodothyronine - T_3 and tetra-iodothyronine - T_4) begins with the transport of iodine ions (J^-) into the cells of the thyroid gland. Iodine is then oxidized under the action of thyroperoxidase into elemental iodine (J°) and binds to molecules of the amino acid tyrosine. This process is called *organization* of iodine. The iodinated tyrosine is now incorporated into thyroglobulin, the protein that forms the main constituent of the colloid of the thyroid follicle. Other iodinated tyrosine molecules attach to the already incorporated tyrosine molecules, forming T_3 or T_4. When T_3 and T_4 are to be released into the circulation, the follicular cells phagocytose the colloid and transport it to their lysosomes. In lysosomes, thyroglobulin is broken down and releases T_3 and T_4, which go into the bloodstream (the ratio of T_4 and T_3 is 5:1). In the blood, the greater part of these hormones is bound to globulins (99.5%), and the smaller part is free and active. T_4 is converted into T_3 in the tissues, which is the active form

of the hormone. T4 and T_3 enter the cells they act on, bind to their receptors in the nucleus and cause the expression of genes for numerous enzymes and functional proteins.

Some drugs (ipodate, corticosteroids, beta-blockers), as well as severe diseases or starvation, inhibit 5'-deiodinase, which normally converts T_4 to T_3. Because of this, the greater part of T_4 is converted into the inactive form of T_3, the so-called reverse triiodothyronine (rT_3), leading to a reduction in the effect on target tissues.

The secretion of thyroid hormones is under the control of pituitary thyroid-stimulating hormone (TSH). This hormone stimulates the enzyme adenylate cyclase in thyroid cells and thus increases the synthesis and secretion of T_4 and T_3. The secretion of TSH itself is controlled by the hypothalamic hormone, TRH (thyrotropin-releasing hormone), whose release depends on the level of T_4 and T_3 in the blood (negative feedback loop).

Thyroid hormones enable the synthesis of many enzymes necessary for the normal functioning of cells. Their presence is necessary for the normal functioning of the STH hormone (and therefore growth); the processes of oxidative metabolism 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 thereby sensitize peripheral tissues to the action of catecholamines.

Thyroid hormones are used to treat hypothyroidism and goiter. Most often, T_4 is administered orally. Therapy should be started with small doses, and then gradually increased, so that the vital organs (first of all, the heart) gradually adapt to the new metabolic needs. The usual dose is 100 - 150 μg /24 hours, orally. T_3 is administered only to patients in a myxedema (hypothyroid) coma, in the form of an intravenous injection (10 μg / 12 hours slowly i.v.). Many authors believe that it is safer to administer T_4 intravenously. In people with heart disease, the use 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 supplemental doses are higher than those normally given.

Hyperthyroidism can be treated in a number of ways. One of them is the use of drugs that inhibit the incorporation of iodine into tyrosine, i.e. synthesis of thyroid hormones. These are thionamides: ***methimazole and propylthiouracil***. These drugs take 3-4 weeks to work, until the hormone depots in the thyroid gland are depleted. Therapy with these drugs lasts about a year, and then it is stopped. In half of the patients, the disease recurs after about a year, so it is necessary to apply the mentioned medicines again. The downside is their tendency to cause neutropenia and other disorders of the blood lines, so during therapy, blood counts should be monitored (any sore throat 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. That is why propylthio - uracil is always used in case of hyperthyroidism in pregnant women. Also, breastfeeding is possible in the presence of propylthioura - cil.

Adverse effects of thionamides occur in about 10% of patients. The most common side effect is maculopapular measles, sometimes accompanied by fever. Rarely, liver damage, swelling of the lymph glands, and symptoms similar to those of 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 (J^{131}), which is now known not to increase the risk of malignant neck diseases. Radioactive iodine is quickly and completely absorbed and then concentrated in the thyroid gland. Only one dose is used, which often leads patients to hypothyroidism, so lifelong replacement therapy with thyroid hormones is necessary. Radioactive iodine must not be used in pregnant women and mothers who are breastfeeding their children, because it passes through the placenta and is excreted in milk.

Iodides in a larger quantity (dose) also suppress the function of the thyroid gland. They reduce the release of thyroid hormones, and an improvement can be noticed as early as 1 day after the start of application. The maximum effect is manifested 3-7 days after the start of application. Also, iodides inhibit organification and reduce blood supply to the gland, which becomes smaller and firmer. That is why iodides are mostly used in the preoperative preparation of patients for whom thyroidectomy is indicated. Side effects of iodide are acne on the skin, swelling of the salivary glands and a metallic taste in the mouth.

Iodides cannot be used alone to treat hyperthyroidism for a long period of time. After 2-8 weeks, the effect wears off, and then a very severe form of hyperthyroidism occurs 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. Then the effects of thyroid hormones on the heart should be *quickly* suppressed. This is achieved by using β-blockers (e.g. propranolol, 1 mg and v., repeat if necessary several more times) that eliminate the influence of catecholamines (T_3 and T_4 otherwise increase the sensitivity of the heart to catecholamines) and iodine contrast agents that block the peripheral conversion of T_4 into the active form of T_3.

Iodides are also used (which after one day noticeably reduce the release of thyroid hormones /0.5 ml /8 hours of Lugol's solution, orally/) and large doses of corticosteroids (eg dexamethasone 4 mg /6 hours orally). In addition to all that, the patient must have quality care, fluid and electrolyte replacement, and nutrition.

Table 17. Doses of antithyroid drugs

MEDICINE	METHOD OF APPLICATIO N	DOSE	GET IT INTERVAL
Methimazole	orally	10 mg	8 hours
Propylthiouracil	orally	200 mg	8 hours
Ipodate (iodine contrast agent)	orally	0.5 g	24 hours*

* It is given only during three days.

ADRENAL CORTEX HORMONES

The adrenal cortex has three layers, from the outside to the inside: 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 simultaneously the secretion of potassium ions in the distal kidney tubules. Aldosterone secretion is mostly controlled by angiotensin 2; a higher level of this peptide in the blood means a higher secretion of aldosterone. Namely, the increased loss of sodium in the kidney tubules leads to the release of renin, which then leads to the creation of angiotensin 1; angiotensin 1 is converted into angiotensin 2 under the action of peptidyl-dipeptidase in the lungs, which in turn increases the secretion of aldosterone. Only a small part of aldosterone secretion is under the control of the pituitary hormone A CTH . Insufficient secretion of aldosterone (Addison's disease) is treated using a synthetic steroid with mineralocorticoid action: fludrocortisone (dose: 0.1 mg /24 hours , orally).

Cortisol and other glucocorticoids, as lipophilic substances, easily diffuse through the cell membrane on which they act. In their cytoplasm, there is a receptor for cortisol, which in its resting state is bound to two molecules, the so-called heat-shock protein (heat-shock protein) which is labeled with Hsp90. With the arrival of cortisol, Hsp90 dissociates from the receptor, and cortisol binds to it. The cortisol-receptor complex then travels to the nucleus and binds to the promoters of a number of genes. By binding to promoters, these complexes actually activate the transcription of those 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; it takes up to 24 hours for the effects to fully manifest.

Cortisol inhibits glycolysis, increases glycogen synthesis in the fasting phase, intensifies glyconeogenesis in the liver and increases blood glucose levels. It also promotes lipolysis and proteolysis in muscle and fat tissue, increasing the supply of free fatty acids and amino acids to the liver. The purpose of the action of cortisol in the period between two meals is to ensure sufficient amounts of glucose in the blood needed to nourish the brain. In addition to metabolic effects, cortisol exhibits the following effects:

a) **anti-inflammatory** (blocks phospholipase A $_2$, 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 means of which leukocytes leave the 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 large doses reduces the formation of antibodies)

d) **antineoplastic** (reduces the number of pathological lymphocytes)

e) decrease in the number of lymphocytes, eosinophils, basophils and monocytes, and increase in the number of neutrophils, platelets and erythrocytes in the blood

f) has **a catabolic** effect on connective tissue, skin, bone tissue, muscles and fat tissue

d) increased concentration of cortisol in the blood initially leads to **insomnia and euphoria**, and later to depression; extremely high doses of glucocorticoids can lead to an increase in intracranial pressure

h) Cortisol is necessary for the normal maturation of surfactant in the lungs of the fetus, during the last weeks of gestation.

Although cortisol is also used as a medicine (hydrocortisone), a large number of preparations with glucocorticoid action have been synthesized. The most used are: ***prednisone*** (which is converted in the liver to its active form, prednisolone) orally, ***prednisolone*** (4 times stronger than cortisol) orally, ***methylprednisolone*** (5 times stronger than cortisol) orally and parenterally, ***dexamethasone*** (40 times stronger than cortisol, no mineralocorticoid effect) 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 to treat macular edema in diabetics. ***Clobetasol*** (ultra-potent corticosteroid), ***fluocinonide and betamethasone*** (high-potency), and ***triamcinolone acetonide*** (moderate-potency) are used locally in the form of ointments or creams for the treatment of skin diseases.

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), lymphatic leukemias and to prevent transplant rejection. Cortisol is also used in the treatment of congenital hyperplasia of the adrenal cortex; hyperplasia occurs due to deficient synthesis of cortisol and consequent greater secretion of A CTH. Near the end of pregnancy, corticosteroids can accelerate lung maturation (increase surfactant synthesis) and prevent respiratory distress syndrome in the child if premature delivery occurs.

Used in large (pharmacological) doses, corticosteroids have many side effects. They increase acid secretion in the stomach, lead to osteoporosis, skin atrophy, psychotic manifestations, hypertension, cataracts and adrenal atrophy (due to suppression of A CTH release). The risk of infections with fungi, viruses and mycobacteria is increasing. Unwanted effects occur after prolonged use of corticosteroids; application for up to 7 days is not associated with significant side effects. When corticosteroids are used for a long time, the cessation of therapy must be gradual, otherwise symptoms and signs of adrenal insufficiency may occur.

When used in the first trimester of pregnancy, corticosteroids increase the risk of cleft palate. If the systemic administration of corticosteroids during pregnancy is necessary due to the nature of the mother's illness, the drug of choice is ***prednisone,*** because it cannot be converted into its active form prednisolone in the fetus's liver, so the fetus is less exposed to harmful effects than if other corticosteroids are used.

Androstenedione and dihydroepiandrosterone secreted in the zona reticularis normally make up a small fraction of the total androgens of men and women. In postmenopause, they become the main source from which estrogens are created by aromatization in fatty tissue.

The synthesis of all adrenal hormones can be completely blocked **by aminoglutethimide**, an enzyme blocker that converts cholesterol to pregnenolone, the first step in steroid synthesis. This effect is used to treat some hormone-dependent tumors of the prostate or breast. **Mitotan** is a drug that destroys the cells of the adrenal cortex; it is used for the palliative treatment of inoperable cancers of the adrenal cortex. 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 N_2 receptor blocker cimetidine and the proton pump blocker omeprazole.

Table 18. Dose of corticosteroids according to indications

MEDICINE	INDICATION	METHOD OF APPLICATION	DOSE
Cortisol (hydrocortisone)	Addison's disease	orally	10 mg /12 hours
Hydrocortisone-Na succinate	Addison's crisis (acute adrenal insufficiency)	and . c .	50 mg / 6 hours
Prednisone	Bronchial asthma	orally	30 mg /day
	Systemic lupus erythematosus	orally	30 mg /day
Methylprednisolone - Na succinate	Anaphylactic shock	and . c .	40 mg
Dexamethasone	Brain edema	and . m .	20 mg /day

ESTROGENS

Estrogens are steroid hormones that are secreted in the ovary (especially in the 1st phase of the menstrual cycle), and during pregnancy and in the placenta. Natural estrogens are estradiol, estrone and estriol. A large number of preparations with estrogenic action have been synthesized, some of which are steroidal (ethinyl-estradiol, mestranol) and some are not (diethyl-stilbestrol, chlorotrianisen).

Estrogens bind to their intracellular receptors, which together (in a complex) regulate the synthesis of a large number of enzymes and structural proteins. The effects of estrogen are:

- trophically effect on the uterus , vagina , vulva and skin nothing at all ;
- stimulation growth ductus dairy glands ;
- in the 1st phase menstrual cycle estrogens bring to growth endometrium ;
- slowing down resorption bones ;
- increase HDL in blood and fall LDL lipoprotein (anti - arte riosclerotic effect);
- increase in the level of coagulation factors in the blood.

Estrogens are used as ***replacement therapy in postmenopause*** because they prevent osteoporosis and eliminate climacteric complaints (hot flashes, irritability, instability of the autonomic nervous system). Their use for this indication should be limited to the age of 60, because in older women they increase the risk of thromboembolism and breast cancer too much. If a menopausal woman only has local symptoms due to atrophic changes in the vagina and trigone of the urinary bladder, then it is sufficient to apply only vaginal preparations with low concentrations of estrogen. In women in the reproductive period, estrogens can stop menorrhagia or metrorrhagia. Estrogens can also suppress the growth of prostate tumors and some breast tumors. Together with progestogens, they are used as oral contraceptives.

Side effects of estrogen are: increased frequency 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 already during the first passage through the liver, so none of

the drug would reach the systemic circulation. Synthetic estrogens or conjugated natural estrogens break down much more slowly, so their oral administration is possible.

Table 19. Doses of the most commonly used estrogens

MEDICINE	METHOD OF APPLICATIO N	DOSES	GET IT INTERVAL
Chlorotrianisen	orally	12 mg	24 hours
Conjugated estrogens	orally	0.5 mg	24 hours
Estradiol cypionate (depot preparation)	and . m .	1.5 mg	4 weeks

PROGESTAGENS

Progestagens are substances that act similarly to the natural ovarian hormone - progesterone. The most similar to progesterone are steroids with 21S-atom (***medroxyprogesterone, megestrol***); another large group of progestogens consists of 19-nortestosterone derivatives (***norethindrone, norethisterone, norgestrel***). One derivative of spironolactone, ***drospirenone, also belongs to progestogens***. Progesterone and progestagens work by binding to their intracellular receptors and regulating gene expression.

Progesterone raises the body temperature, has a depressing effect on the central nervous system, promotes the development of the alveoli of the mammary gland and the secretory maturation of the endometrium in the 2nd phase of the menstrual cycle. It also relaxes smooth muscles.

Progestogens are used to treat irregular menstrual bleeding, to treat endometriosis, and to treat dysmenorrhea. They are also an integral part of combined estrogen-gestagen preparations for hormone replacement in postmenopause and for contraception.

Progesterone should not be used during pregnancy because it increases the frequency of hypospadias in male newborns! In non-pregnant women, progesterone can cause depression and edema. Derivatives of 19-nortestosterone have significant androgenic side effects: they can cause hirsutism (increased male pattern baldness), acne, skin pigmentation, reduction of HDL lipoprotein levels in plasma. That's why a new generation of progestagens was synthesized that have a weaker androgenic effect and do not affect estrogen receptors either: dienogest, drospirenone, nestorone, nomegestrol acetate and trimegestone. Some of the new progestogens even block androgen receptors: ***dienogest, drospirenone and trimegestone***.

Table 20. Doses of the most commonly used progestogens

MEDICINE	METHOD OF APPLICATI ON	DOSE	DOSE INTERVAL	INDICATION
Medroxy-progesterone-acetate	orally	5 mg	24 hours	Disorders of menstrual bleeding
	and . m . (depot)	500 mg	7 days	Some types of breast cancer
Progesterone	and . m .	10 mg	24 hours	Disorders of menstrual bleeding
Norethisterone	orally	5 mg	12 h (from the 5th day of the 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 per day for 4 days is given. Also, it can be used effectively for post-coital contraception: just one dose of 600 mg immediately after coitus can prevent fertilization of the ovum 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 it prevents the proliferation of the endometrium, prevents the further growth of uterine fibroids, and reduces the secretion of gonadotropins in the pituitary gland. It is primarily used to calm the symptoms of uterine fibroids (prolonged bleeding) before surgery or occasionally in patients who are not candidates for surgery. The drug is well tolerated, because of the side

effects it has only redness of the face and neck with a feeling of heat, and thickening of the endometrium, which 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 to treat menopausal women with metastatic or locally advanced estrogen-dependent breast cancer, provided that the disease has not responded to other anti-estrogen drugs. It is administered intramuscularly, in one dose per month. Adverse effects are thromboembolism and liver damage with an increase in 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 and have no effect in others. They are synthesized with the idea of creating drugs that will have the desirable effects of estrogen, but will not exhibit the unwanted effects characteristic of estrogens.

The first estrogen receptor modulator was ***tamoxifen***. It is used to treat breast tumors that are dependent on estrogen, i.e. which have estrogen receptors in their cells, primarily in postmenopausal women. It is administered orally, in a dose of 10 mg /12 hours. Side effects of tamoxifen are vomiting and "hot flashes".

Raloxifene is a selective estrogen receptor modulator used to treat osteoporosis in perimenopausal women, as it reduces bone breakdown. It is also used to reduce the risk of invasive breast cancer in postmenopausal women, if they are otherwise at high risk. Raloxifene can cause venous thrombosis and stroke with fatal outcome.

Ospemifene acts as an estrogen receptor agonist in the vulva, vagina and bones, as a receptor antagonist in the breast and as a partial receptor agonist in the uterus. This effect profile enables its use in the treatment of vulvo-vaginal atrophy in menopausal women, which otherwise greatly reduces the quality of life. Ospemifene is administered orally, and has few side effects, of which "hot flashes" are the most common.

Clomiphene blocks estrogen receptors in the pituitary gland, leading to increased release of gonadotropins. This mechanism of action is the reason for using clomiphene to stimulate ovulation in women who are being treated for infertility. Adverse effects of clomiphene include ovarian enlargement, "hot flashes" and nausea.

AROMATASE INHIBITORS

Aromatase is an enzyme found in adipose tissue, muscles, liver and mammary gland; this enzyme converts the androgen androstenedione into estriol, which is the main source of estrogen in menopausal women. Drugs that inhibit aromatase can be used as adjunctive therapy for breast cancer (both in early stage and advanced disease) in menopausal women (provided the cancer contains estrogen receptors). Until recently, aminoglutethimide, a drug that simultaneously blocks the synthesis of steroid hormones in the adrenal cortex, was used for these purposes. Today, there are selective aromatase inhibitors that have few side effects and are effective. Some of such drugs are ***letrozole, anastrozole and exemestane***. The common non - desired effect of these three drugs is osteoporosis; letrozole and anastrozole cause hypercholesterolemia in addition to osteoporosis.

ORAL CONTRACEPTIVES

Oral administration of estrogen, progestagen, or a combination of estrogen and progestagen can effectively prevent conception. Since the use of only estrogen is associated with too high a risk of side effects, today only a combination of estrogen and progestagen or only progestogens are used. The combination of estrogen and progestagen inhibits the release of FSH and LH from the pituitary gland and thus prevents ovulation; the endometrium becomes inhospitable for zygote implantation, and the cervical mucus remains thick throughout the cycle. The combination is taken from the 7th day after the start of menstruation until the 28th day. After the cessation of taking, menstruation occurs, and taking the preparation continues in the next cycle.

The preparation with only progestagen is taken continuously, without a break. Progestagen makes the endometrium inhospitable to the zygote, and the cervical mucus thick and impenetrable to spermatozoa. Although it is inhibited by the release of LH from the pituitary gland, progestagen preparations prevent ovulation in only 40 % of cycles. Despite the constant use of progestagen, irregular menstrual bleeding occasionally occurs.

Combined preparations prevent conception in 99% of cases and preparations with only progestagen in 97%.

Unwanted effects of estrogen from contraceptive preparations are: an increase in the coagulation factor in the blood (thus a greater tendency to arterial and venous thrombosis), an increase in blood lipids, migraine headaches, hypertension, enlargement of uterine fibroids, fibrocystic breast disease, the appearance of telangiectasias and a carcinogenic effect on the cervix uterus and

breast. Adverse effects due to progestagen are: depression, increased appetite, acne, hirsutism, jaundice, reduced level of HDL lipoprotein in the blood, cervicitis and fluid retention.

Contraindications for the use of oral contraception are: pregnancy, vascular disorders and cancer of the breast or endometrium. Oral contraceptives should not be given to women in the first two years after the first menstruation (menarche) , because there may be disturbances in menstrual cycles after the cessation of use and a slightly higher frequency of sterility than in the general population. Also, women over the age of 40 should not take these agents because of the high risk of thrombosis (venous thrombosis, myocardial or brain infarction) and hypertension. The risk is especially high for women who are smokers.

A special type of oral contraception is postcoital contraception. In the first 72 hours after coitus, conception can be prevented if large doses of estrogen (eg ethinyl estradiol, 2.5 mg /12 hours, for 5 days) or progestagen (eg levonorgestrel , 0.75 mg postcoital) are used . This is of great importance in unwanted conception due to rape and other circumstances.

Table 21. Examples of oral contraceptives

MEDICINE	COMMENT	USE
Norethisterone (0.5 mg) + ethinyl estradiol (0.035 mg)	A combination of progestagen and estrogen	1 tablet/day from the 7th to the 28th day of the menstrual cycle
Levonorgesterol	Progestagen	1 tablet of 0.75 mg postcoital

ANDROGEN AND ANABOLIC STEROIDS

The main natural androgen in the human body is testosterone, which is secreted in the testicles and (in a very small amount) in the adrenal cortex. The other two natural androgens, dehydroepi-androsterone and androstenedione, are produced primarily in the adrenal cortex; they are significantly less effective 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 follicle, seminal vesicles and epididymis), the active metabolite of testosterone, 5-dihydrotestosterone, binds to the androgen receptor α.

Androgens affect the development of secondary characteristics of the male sex (slackness, deep voice, alopecia, muscularity...), accelerate the incorporation of amino acids into the striated muscles (lead 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 short-term treatment of reduced sexual desire. Testosterone is administered intramuscularly as testosterone enanthate or cypionate, or transdermally using special patches.

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 muscles and stimulate erythropoiesis, just like natural androgens, but to a much lesser extent they cause masculinization. Such compounds are called anabolic steroids (these are: ***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.

Adverse effects of androgens and anabolic steroids are:

- masculinization the code woman ,
- cholestatic jaundice ,
- lowering of HDL lipoproteins,
- acne on the skin ,
- aggressive behavior and
- retention of sodium .

Table 22. Dose of androgens and anabolic steroids

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL	INDICATION
Testosterone	and . m .	25 mg	3 days	Substitution therapy
Stanozolol	orally	2 mg	12 o'clock	Congenital angioedema
Nandrolone Decanoate	and . m .	25 mg	1 month	Cachexia

ANTIANDROGENS

Blockade of the effect of androgens can be achieved most easily by blocking their receptors or by blocking the production of the active form of testosterone: 5 α-dihydrotestosterone.

The first drug shown to block androgen receptors was ***spironolactone*** (which also blocks aldosterone receptors). Later on***, cypro-terone-acetate*** was discovered and then flutamide. Today we have at our disposal three effective androgen receptor blockers: **flutamide, bicalutamide and nilutamide**. All three mentioned drugs are successfully used in the treatment of hirsutism and advanced androgen-dependent prostate cancer. Side effects of flutamide and bicalutamide are not very common; the most serious occurrence is toxic hepatitis, which is reversible. Gynecomastia may also occur.

Finasteride successfully inhibits the 5 α-reductase enzyme that converts testosterone into 5 -dihydrotestosterone α. Since 5 α-dihydrotestosterone is important for androgenic effects in the prostate and hair follicle, 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 disturbances. The dose 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 to see the effect.

TREATMENT OF BENIGN PROSTATE HYPERPLASIA

Before prostatic hyperplasia becomes so large that it causes complications (urine 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 sphincter of the urethra and the smooth muscles of the prostate, making urination easier (improves urine flow). The following -blockers are most commonly used for this indication α: doxazosin, alfluzosin, indoramin, prazosin, terazosin and tamsulosin. They must be applied carefully: the first dose is given before bedtime, in order to avoid the consequences of very pronounced hypotension; later, the body gets used to $\alpha$the -blocker, but occasionally orthostatic hypotension can occur, especially when standing up suddenly. In addition to hypotension, α-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 5 α-reductase, the enzyme that converts testosterone to dihydrotestosterone. In the prostate, dihydrotestosterone is much more active than testosterone itself, and leads to hyperplasia. By using finasteride for several months, it is possible to achieve reduction of the prostate, and thus the elimination of complaints (difficulty urinating).

Finasteride is administered in a dose of 5 mg /day, orally. Due to disruption of normal testosterone metabolism, finasteride has significant side effects: impotence, ejaculation disorders, gynecomastia, reduced libido.

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 androgenic 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 higher structures that control reflex arc activity). Regardless of the cause, impotence can be successfully treated with several medications:

1. ***Prostaglandin E 1*** (alprostadil) can be injected into the corpora cavernosa or applied transurethrally, in the form of a cream. In both cases, alprostadil leads to vasodilation and relaxation of the corpus cavernosum, which allows for a sudden influx of blood and slowed swelling, i.e. erection. Erection occurs regardless of the presence or absence of sexual excitement, and lasts 20-60 minutes. In that time, it is possible to achieve penetration. The downsides of this type of therapy are the complicated application, the appearance of hematoma on the penis, priapism (prolonged and painful erection, over 6 hours) and, sometimes, the appearance of fibrosis of the corpora cavernosa.
2. ***Sildenafil*** (Pfizer's Viagra product) ®is a selective inhibitor of phosphodiesterase-type V, which is found in penile tissues. As a result of this inhibition , there is an accumulation of cyclic guanosine monophosphate, but only if, as a result of sexual arousal, the release of nitric oxide (NO) from the nerve structures of the penis is enhanced (NO stimulates guanylate cyclase and increases the creation of cGMP). Accumulation of cGMP leads to relaxation of the corpora cavernosa, which allows a sudden influx of blood and results in an erection. In order to achieve the desired effect, one should take a 50 mg tablet one hour before coitus. The half-life of sildenafil is 3-5 hours. Side effects of sildenafil are color vision disorders , headache, facial flushing and hypotension. Simultaneous administration of sildenafil with nitrates or other vasodilators is contraindicated because extreme hypotension, reduction of perfusion through coronary arteries and myocardial infarction may occur.
3. Besides sildenafil, two more phosphodiesterase type 5 blockers have come into use: ***tadalafil and vardenafil***. While vardenafil is very similar to sildenafil in everything, tadalafil is characterized by slow absorption from the digestive tract, but also a longer duration of action. While the effect of silda nafil and vardenafil lasts for several hours, tadalafil still has an effect 36 hours after the dose taken.
4. Recently, ***apomorfin has been used to treat impotence***. It is applied in the form of a lingual tablet, 2 mg about 20 minutes before the sexual act. The next dose of apomorphine can only be administered after more than 8 hours have passed. Like the other two impotence drugs, apomorphine increases blood flow to the corpora cavernosa of the penis. Apomorphine causes vasodilatation and hypotension, so it should be avoided in people with heart failure or coronary disease, as it may worsen . Vaso-vagal syndrome, which apomorphine sometimes provokes, also has a very unpleasant effect: sweating and heartburn .

MELATONIN

Melatonin is a hormone of the pineal gland. According to its chemical composition, serotonin is methylated and acetylated. Its secretion during the waking state is inhibited by the tonic activity of the retino-hypothalamic tract. During the night, when the activity of this pathway decreases, the secretion of melatonin increases significantly. In lower animals, melatonin can change skin color and thus enable adaptation to living conditions with less light. In humans, melatonin facilitates the normal transition between wakefulness and sleep, and has a general hypnotic effect. That's why it is used therapeutically to establish a normal rhythm of waking state - sleep in people who have suddenly changed the time zone (eg after a plane flight from Europe to America) or who are forced to work in the night shift. Adverse effects of melato-nin are currently unknown. Although the immune-stimulating and antioxidant role of melatonin is insisted, there is still no reliable evidence for these claims.

Melatonin is also used to treat insomnia that is not related to the disturbance of the day-night rhythm of exposure to light. It successfully prolongs sleep, facilitates falling asleep and increases the quality of sleep, so that the patient is more rested after waking up.

The side effects of melatonin are relatively mild: sleepiness the next day, moodiness, 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, through the hypothalamus, ghrelin increases the secretion of growth hormone from the pituitary gland. In summary, since ghrelin leads to an increase in appetite and greater food intake, and also has an anti-inflammatory effect, it has great potential for the treatment of cachexia in chronic diseases. Clinical studies with ghrelin and its oral analogue anemorelin are ongoing.

MEGESTROL

Megestrol is a progesterone analogue whose exact mechanism of action is not known, but it has been used for several decades to treat cachexia and anorexia in patients with acquired immunodeficiency syndrome or with malignant tumors. Its effectiveness has recently been questioned after a systematic review of published clinical studies. Among the side effects, megestrol causes thromboembolism, transient adrenal insufficiency, hypogonadism, edema and confusion.

AND PHOSPHORUS METABOLISM

Calcium and phosphorus in the form of phosphates are necessary for the performance of 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 kidney tubules. This ensures the optimal level of calcium and phosphate in the blood, necessary for normal bone mineralization. Parathormone (hormone of the parathyroid gland) increases the activity of osteoclasts, i.e. increases bone resorption and facilitates the conversion of vitamin D into an active form in the kidney. In addition, this hormone increases calcium reabsorption and prevents phosphate reabsorption in kidney tubules. The ultimate effect of PTH 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%), bound to organic anions (3%, citrate, lactate) and free, ionized (about 47%; it is the active form of calcium). The total concentration of calcium in the blood is about 2.5 mM / l and phosphate about 1 mM / l.

A reduced level of calcium in the blood (hypocalcemia) leads to spasms of the striated muscles (tetany). In EC G, prolongation of the QT interval can be seen. Severe hypocalcemia is treated with slow intravenous administration (longer than 20 ') of calcium gluconate (10 ml of 10% solution) or chloride. On the other hand, chronic calcium replacement is performed by oral administration of calcium carbonate (1-2 g per day).

Hypercalcemia (very common in generalized malignant diseases) primarily affects the functioning of the CNS. First there is confusion, then somnolence, drowsiness and coma. In EC G, the Q-T interval is shortened. Hypercalcemia is primarily treated with the use of Henle's loop diuretics together with saline infusions (0.9% NaCl 4 l /24 hours + 125 mg furosemide i.v.). Calcitonin, the hormone of C -cells of the thyroid gland, can also be used, which inhibits the activity of osteoclasts (dose: 8 I J/ kg /8 hours and m .).

Vitamin D exists in two forms: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholesterol is oxidized in the intestinal epithelium into 7-dehydrocholesterol; dehydro-cholesterol is converted into cholecalciferol in the skin under the influence of UV light. Ergocalciferol is part of the cell membranes of plants and is taken in through 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 are active forms of vitamin D.

Deficiency of vitamin D leads to defective mineralization of bones, which is manifested by rickets in children and osteomalacia in adults. That is why vitamin D is given prophylactically to children in the first two years of life, in order to prevent the occurrence of rickets. The daily dose is 400 IJ. In significantly higher doses, vitamin D can be used to treat rickets and osteomalacia.

H -derivative of vitamin D is prevented , so there is a deficit of the active form of the vitamin and defective bone mineralization - the so-called. renal osteodystrophy. For its treatment, ***calcitriol*** (1,25-(OH) 2 $_{-vitamin}$ D) or ***1-- αcalcidiol*** (a synthetic analog of vitamin D that is hydroxylated at position 1 αand becomes active after additional 25-hydroxylation in the liver) is used , because both of these forms do not need to be hydroxylated in the kidney. The calcitriol derivative ***paricalcitol*** (19-nor-1,25- dihydroxy vitamin D_2) is even more effective than calcitriol in the treatment of renal osteodystrophy, because it lowers the parathormone concentration in the blood more quickly, disturbs the serum levels of calcium and phosphate less, and also works in patients with high by serum phosphate concentration. It has also been shown that the survival of patients receiving paricalcitol is longer than the survival of patients treated with calcitriol.

If overdosed, vitamin D has a toxic effect (hyper-vitaminosis D). Hypercalcemia and hypercalciuria occur.

Hypoparathyroidism most often occurs after surgical removal of the thyroid gland, when the parathyroid glands are removed together with it . Hypocalcemia occurs, which is treated with calcium and vitamin D preparations (50,000 IU of vitamin D, 3 times a week + 1 g of $SaSO_3$/day). Hyperparathyroidism is treated surgically - by removing the tumor or hyperplasia of the parathyroid.

Osteoporosis is a loss of bone mass: both the bone matrix and mineral substances together. It occurs in old age, in women after menopause and after long-term use of corticosteroids. It is the cause of the increased frequency of fractures and bone pain. Although **calcitonin** (which inhibits the activity of osteoclasts) can also be used for its treatment, today it is more effective to use bisphosphonates. Bisphosphonates are pyrophosphate analogs that have a carbon atom instead of oxygen: -R-S-R- instead of -R-O-R-. They are deposited in bones, stabilize hydroxyapatite and prevent bone resorption. Thus, synthesis processes overcome resorption processes and osteoporosis is improved. ***Etidronate, pamidronate, alendronate, ibandronate, zolendronate*** 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 dental implants falling out. Also, orally applied bisphosphonates have an irritating effect on the mucous membrane of the esophagus, so they must be taken with plenty of water, and the patient should remain in an upright position for at least 1 hour after swallowing the tablet. When bisphosphonates are administered parenterally (eg pamidronate, zolendronate or ibandronate), they show **a nephrotoxic** effect in 5-10% of patients. The nephrotoxic effect can be partially avoided if the patient is well hydrated.

Osteoporosis in postmenopause can also be successfully stopped with the use of estrogen (e.g. 25 μg of ethinyl-estradiol per day) or raloxifene over several years. In order to reduce the risk of endometrial cancer, a progestogen (eg 2.5 mg of medroxyprogesterone per day) is administered at the same time.

Today, we have at our disposal three more very effective drugs for osteoporosis, which we use when bisphosphonates no longer work. One is ***denosumab***, a monoclonal antibody against the factor RANKL (ligand of the activator receptor of nuclear factor kappa B), which, by neutralizing the said factor, leads to reduced osteoclast activity. RANKL otherwise stimulates the proliferation and activity of osteoclasts. Denosumab is administered subcutaneously, once every 6 months. It has shown greater effectiveness 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 smaller number of patients the risk of skin and subcutaneous tissue infections increases, and osteonecrosis of the jaw may also occur.

Another, even more effective drug for osteoporosis, is ***teriparatide***, an active fragment (1-34) of parathormone, which directly stimulates osteoblast activity in bones, and indirectly increases calcium absorption in the intestines, and calcium reabsorption and phosphate excretion in kidney tubules. It is the only drug that can not only stop osteoporosis, but also increase bone density. It significantly reduces the frequency of vertebral fractures, but not femur fractures. Teriparatide is administered subcutaneously, once a day. Among the side effects, the drug causes pain in the extremities, anemia, depression and hypotension.

The third drug for osteoporosis, which has only recently come into use, is another monoclonal antibody ***romosozumab*** , this time against sclerostin. The protein sclerostin is produced by osteocytes, and its function is to increase the breakdown and decrease the formation of bone. Romosozumab blocks the action of sclerostin and thus leads to an increase in bone density. It is applied subcutaneously once a month, and after one year it leads to an increase in bone density by several percent in women with osteoporosis in menopause, and reduces the frequency of compression fractures of the spinal vertebrae in the same population. It is also effective in men with osteoporosis. Osteonecrosis of the jaw occurs very rarely when using this drug. Romosozumab must not be given to people who have had a myocardial infarction or stroke in the previous year, as it increases the risk of recurrence of such complications.

PHARMACOLOGY OF BLOOD AND TISSUES

ANTICOAGULANT THERAPY

Normal blood coagulability is necessary to maintain blood in blood vessels and the heart. Sometimes there is inadequate and excessive activation of the coagulation system and the formation of thrombus inside the blood vessels. A thrombus is made of a fibrin network in which blood cells are caught: primarily platelets, then erythrocytes and leukocytes. A thrombus in arteries (where the blood flow is fast) consists mainly of fibrin and platelets (so-called white thrombus), and a thrombus in veins also has many erythrocytes (red thrombus).

Medicines that can reduce blood coagulability can also prevent the formation of thrombus.

Oral anticoagulants. These are drugs that inhibit the reduction of vitamin K in the liver. Reduced vitamin K is necessary for 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 are either coumarin derivatives (warfarin, acenocoumarol) or indanedione derivatives (phenin-dione). Indandione derivatives are as effective as coumarin derivatives, but significantly more toxic; therefore, coumarin derivatives are preferred in practice. They are well absorbed from the digestive tract, penetrate into all tissues, are metabolized in the liver, and the metabolites are excreted in the urine. They pass through the placenta and have a teratogenic effect; therefore they are not used in pregnancy. 1-3 days must pass from the start of application to the start of the effect, which is how long the already synthesized coagulation factors in the blood should be used up. During this time, we can protect the patient with heparin, which we discontinue after the effect of oral anticoagulants begins.

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 P 450, namely isoforms 2 C 9 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 mentioned forms of cytochrome. Therefore, when prescribing other drugs to patients who are on chronic therapy with oral anticoagulants, the doctor should always consult the reference literature, check the possibility of interactions and adjust the dose of the drugs accordingly.

Oral anticoagulants are used to treat deep vein thrombosis, **for prevention** and treatment of pulmonary embolism, for the prevention of thrombosis after implantation of artificial valves in the heart and for the prevention of 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 are dosed individually, based on prothrombin time control. The effect of oral anticoagulants on prothrombin time is today expressed through INR (International Normalized ratio). It is the ratio of the prothrombin time of the patient and the control, where both times were obtained using the 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, an antidote - vitamin K - should be administered. From 12 to 24 hours after its application, the normalization of coagulation occurs. If it is necessary to normalize coagulation urgently (for example, in case of heavy bleeding), this can be done by applying fresh plasma or coagulation factor concentrate.

Adverse effects are: occurrence of bleeding in the digestive tract and CNS, thrombosis of subcutaneous veins with necrosis of fatty tissue (in the breast and gluteal area, due to decreased activity of protein C in the plasma) and, rarely, liver damage. Thrombosis of subcutaneous veins occurs at the very beginning of therapy (in the first 2-3 days), while the anticoagulant effect has not yet been established. Rarely, diarrhea, alopecia, necrosis of the small intestine and livid toes occur.

Oral anticoagulants are contraindicated in all conditions where there is an increased possibility of bleeding with serious consequences: if there is a peptic ulcer, malignant hypertension, bacterial endocarditis, thrombocytopenia and similar conditions.

Heparin. Heparin is a mixture of complex carbohydrates from the group of glycosaminoglycans. 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. Also, heparin increases the inhibitory effect of cofactor 2 on thrombin. Its action begins immediately after application.

Parenteral administration of heparin is allowed only intravenously or subcutaneously; intramuscular injection is avoided, as hematoma formation at the injection site may occur.

Heparin is partly metabolized in the liver (in the reticuloendothelial system), and partly eliminated unchanged through the kidneys ($T_{1/2} \approx 90$ minutes).

Heparin is used for the treatment and prevention of deep vein thrombosis and as prophylaxis of thrombosis of vascular grafts after their installation. In addition, it is used in the prophylaxis and treatment of embolism, in the prevention of postoperative venous thrombosis and as an additional means 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 it is necessary to apply anticoagulant therapy for a long time, then it is necessary to switch to oral anticoagulants soon after the introduction of heparin. Oral anticoagulants are usually started at the same time as heparin; as soon as their effect begins, the administration of heparin is stopped. Heparin should not be administered for longer than 7 days, because side effects are more common then.

If heparin is administered therapeutically, the dose is 5-10,000 I J/6 hours intravenously. In the prophylaxis of deep venous thrombosis (for example after major surgical procedures) it is administered subcutaneously, in a dose of 5000 I J/12 hours. The dose of heparin is adjusted according to the value of the activated partial thromboplastin time (a P TT); and P TT 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 using an antidote - protamin sulfate, which binds to heparin through ionic bonds and inactivates it. For every 100 IJ of heparin administered, 1 mg of protamine sulfate should be given.

The most common side 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 the administration of heparin, and is transient in nature. "Delayed" thrombocytopenia is a consequence of the creation of antibodies against platelets whose action depends on heparin, so that the platelets are destroyed by the action of the antibodies. Delayed thrombocytopenia is accompanied by thrombosis of smaller arteries and subsequent gangrene of the fingertips. These thromboses are treated with drugs that directly inhibit thrombin: argatroban and bivalirudin. In addition to the two already mentioned side effects, heparin can cause fever, alopecia, osteoporosis, bone pain, and hypoaldosteronism. Like oral anticoagulants, heparin should not be given in conditions where there is a tendency to bleeding with severe consequences.

Since heparin does not cross the placental barrier, it can be used during pregnancy.

As its sequence of 5 amino sugars is essential for the effect of heparin, substances containing this sequence and whose molecules are significantly shorter than heparin molecules have been synthesized. These are the so-called ***low molecular weight heparins***. Unlike true heparin, they inhibit the action of factor X only and not other factors. However, clinically, their anticoagulant effect is not weaker than heparin. On the contrary, they have significant advantages over heparin. They do not cause thrombocytopenia and osteoporosis, and after subcutaneous administration their effect lasts longer; due to a more reliable and predictable effect, when these drugs are used it is not necessary to control a P TT, as with the use of ordinary 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 good, above all, 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. Recently, low molecular weight heparins (also called 'fractionated') are also used for the treatment of deep vein thrombosis, unstable angina pectoris and to prevent coagulation in the extracorporeal circulation machine. If low molecular weight heparins are overdosed, protamine sulfate can be used.

The preparation containing only 5 amino sugars is called **fondaparinux**. It directly inhibits factor H, and is used in all indications in which low molecular weight heparins are used: prophylaxis and treatment of deep venous thrombosis and embolism, treatment of unstable angina pectoris and myocardial infarction. It is as effective as low molecular weight heparins, but unlike them, it *rarely causes thrombocytopenia*.

Dabigatran etexilate is a direct thrombin inhibitor that can be taken orally. It is as effective as low molecular weight heparins in the prevention of deep vein thrombosis; monitoring of coagulation tests is not required when dabigatran is used. The only significant side effect of this drug is bleeding. Since recently, dabigatran has been used for the prevention of strokes and embolism in atrial fibrillation, as well as for the treatment of deep vein thrombosis and pulmonary embolism. Dabigatran is mostly excreted unchanged in the urine.

Rivaroxaban and apixaban are direct factor H inhibitors that are used to prevent deep vein thrombosis in orthopedic surgery, to prevent embolization in patients with atrial fibrillation not caused by heart valve disease, and to treat 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 mostly metabolized in the liver by cytochromes, but also by other pathways, to inactive metabolites.

Dabigatran, rivaroxaban and apixaban are called "new oral anticoagulants", to distinguish them from warfarin and other vitamin K antagonists.

Hirudin and medicines derived from it. The anticoa-gulans hirudin is a component of salivary leech (Hirudo medici - nalis). By directly binding to thrombin, it inhibits its action; thereby preventing the formation of fibrin, i.e. thrombus. Hirudin is not used as a medicine, 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 to reduce blood coagulability in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. They are used together with aspirin. For this indication, they showed greater effectiveness than heparin. They are also used to treat venous thrombosis accompanying heparin-induced thrombocytopenia.

The main risk when using these drugs is bleeding; however, bleeding is less frequent than with heparin.

Bivalirudin is administered intravenously. The effect begins immediately after application, and ends 1 hour after the end of application. 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 i low molecular weight heparins

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Warfarin	orally	5 mg	24 hours
Enoxaparin	subcutaneously	2000 and J	24 hours

VITAMIN K

Liposoluble vitamin K exists in two forms: phylloquinone (phytonadione, vitamin K_1), which is found in green leafy vegetables, and menaquinone (vitamin K_2), 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 need for vitamin K is about 1 μg / kg. There is a depot of this vitamin in the liver, which lasts only a few weeks in case of a 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, with malabsorption).

Intravenous administration of vitamin $K_{1\text{ should be avoided}}$ because it can be associated with mast cell degranulation: hypotension, dyspnea, chest and back pain occur. If i.c . application is necessary, then the injection of vitamin K_1 must be *slow* (>20 min).

Synthetic vitamin K (menadione, vitamin K_3), which is water-soluble, must first be converted to vitamin $K_{1\text{ in the liver}}$ in order to work. Therefore, it should be avoided in practice - for example, in case of overdose of oral anticoagulants, menadione is ineffective.

IRON

Iron is found in larger quantities in green vegetables and "red" animal meat, in a divalent (Fe^{2+}) or trivalent (Fe^{3+}) form. In the stomach, under the action of chlorodonic acid, trivalent iron changes to the divalent form (Fe^{2+}), which is much better absorbed in the duodenum and small intestine. Absorption is carried out through a specific transport system in the enterocyte membrane. From the enterocytes, iron is transported to other tissues bound to the plasma protein, transferrin. Iron in its divalent form (Fe^{2+}) is an integral part of heme in hemoglobin and myoglobin, and the cytochrome of all cells. It is necessary for oxygen transport and cellular respiration. Excess iron binds (especially in the liver) to the intracellular protein ferritin; with excessive iron accumulation, ferritin molecules aggregate into a complex known as hemosiderin.

Elimination of iron from the human body is done only by exfoliation of dead cells from the skin and mucous membrane of the digestive and respiratory tract. That's why it is very easy to accumulate iron in the body in case of excessive intake. The daily requirement for iron is about 1 mg.

Iron deficiency is manifested by hypochromic microcytic anemia. Deficiency usually occurs due to chronic loss of small amounts of blood (menstruation in women, hemorrhoids in men), and less often due to insufficient intake.

Iron deficiency in the body can be assessed by measuring the concentration of hemoglobin in the blood, because it is known that 1 L of blood (140 g of hemoglobin) contains about 470 mg of iron. If the patient e.g. has only 100 g of hemoglobin per liter of blood, this means that he lacks:

$$\frac{140-100}{140}\cdot 470mg$$

of iron per liter of blood. Since a person has about 5 L of blood, the obtained amount should be multiplied by 5 and about 500 mg should be added to it to fill the empty depots.

Iron can be administered orally (usually as $FeSO_4$) or intravenously (as Fe -dextran , iron (III) - sucrose hydroxide complex, or iron (III) isomaltoside). Oral administration is simpler, but is associated with irritation of the mucous membrane of the stomach and small intestine. Also, it should be kept in mind that about 10% of the iron intake is absorbed orally. Intravenous administration can provide the total amount of missing iron at once, but a number of people may react with fever, nausea, back pain, facial flushing, or bronchospasm. Therefore, a small test dose (20 mg of iron) is always given for 30 minutes first, and if there is no reaction, continue with the administration of the entire amount ***by*** slow intravenous infusion.

Acute iron poisoning

Acute iron poisoning is common in young children who usually swallow their mother's red-colored iron tablets thinking they are candy. Poisoning takes place in three stages. In the beginning, already after about 60 minutes of taking the tablets, diarrhea, hematemesis and melena occur. Then there is a slight improvement (stage 2), to be followed by damage to the central nervous system with epileptic seizures and coma. In the end, liver failure can occur (stage 3). Sometimes ileus is considered as the fourth stage of poisoning, which can occur weeks after ingestion of the poison due to scar stenosis of the small intestine.

In addition to general measures (rehydration, fight against shock, care), patients are treated with oral (to prevent further absorption of iron) and parenteral administration of deferioxamine chelate.

VITAMIN B $_{12}$ AND FOLIC ACID

Vitamin B $_{12}$ exists in nature as hydroxy- or cyano-cobalamin. Folic acid is reduced in the human body to its active form - tetrahydrofolic acid. Both vitamin B $_{12}$ 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 B $_{12}$ is necessary for the regeneration of tetrahydrofolic acid from methyl tetrahydrofolate. Vitamin B $_{12}$ is also a cofactor of the key reaction in the synthesis of fatty acids: the conversion of methylmalonyl-SoA into succinyl-SoA; due to lack of vitamin B $_{12}$, abnormal fatty acids are formed, which are incorporated into the membranes of nerve cells.

A lot of vitamin B $_{12}$ can be found 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 and called "intrinsic factor". Vitamin B $_{12}$ deficiency usually occurs when the stomach lining is damaged (atrophic gastritis) or removed (eg total gastrectomy, gastric resection). On the other hand, folic acid is found in green vegetables, yeast and animal liver. Folic acid deficiency occurs due to a deficient diet. The daily need for vitamin B $_{12}$ is about 2 μg, and the daily need for folic acid is about 0.5-1 mg. While vitamin B $_{12}$ is deposited in large quantities in the liver (so that even after complete cessation of intake, it takes about 5 years for a deficit to appear), the depot of folic acid is only ten milligrams, so after cessation of intake, symptoms appear after only a few days and deficit signs.

The lack of both vitamin B $_{12}$ and folic acid results in a difficult synthesis of nucleic acids, which is manifested primarily by the appearance of megaloblastic anemia. When it comes to vitamin B $_{12}$, its deficiency not only leads to anemia but also to a neurological disorder - funicular myelosis (degeneration of the dorsal columns of the spinal cord).

Vitamin B $_{12}$ 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 used in megaloblastic anemia unless vitamin B $_{12}$ deficiency has previously been ruled out! Otherwise, the anemia will be cured, and the funicular myelosis will worsen!

Folic acid is routinely administered to all pregnant women in 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, because the risk of spina bifida is higher in their children.

Folic acid and vitamin B $_{12}$ have no side effects, even if used in large doses. All the excess of ingested drugs is excreted in the urine.

HEMATOLOGICAL GROWTH FACTORS

Growth, reproduction and differentiation of blood lineages in the bone marrow are dependent on hormones of a protein nature that are produced in the kidney (erythropoietin) or secreted by lymphocytes (granulocyte and macrophage colony stimulating factor / GM - CSF / and granulocyte colony stimulating factor / G - CSF /). Erythropoietin stimulates the growth of the erythrocyte lineage, G - CSF (another name is **filgrastim**) stimulates the formation of granulocytes, and GM - CSF (another name is **molgramostim**) stimulates the proliferation and differentiation of all blood lineages. The glycosylated form of G - CSF is called **lenograst**.

There are two preparations of erythropoietin - erythropoietin alfa and erythropoietin beta. There is no difference in efficiency between them, but erythropoietin alfa can be administered only intravenously, and erythropoietin beta both intravenously and subcutaneously. The use of erythropoietin alfa subcutaneously was discontinued due to the appearance of erythrocyte lineage aplasia syndrome.

Erythropoietin is used for the treatment of severe anemia in chronic kidney failure, and G - CSF and GM - CSF for accelerating the recovery of the white line of the bone marrow after the use of cytostatics in the treatment of a malignant disease. All three growth factors may be useful in aplastic anemia and other types of bone marrow failure. The erythropoietin analogue, ***darbepoetin α***, differs from erythropoietin in the number of oligo-saccharide 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, in the form of a subcutaneous injection.

An unwanted effect of erythropoietin can be an excessive increase in hematocrit with consequent 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 doping. They use it especially in sports that require endurance, e.g. in cycling, marathon runners and the like. Several deaths have been recorded in athletes who misused it, because the increased number of erythrocytes increases the viscosity of the blood, and thus the tendency to thrombosis and myocardial infarction.

Table 24. Doses of hematological growth factors

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Erythropoietin	and . v ., s . c .	100 IJ / kg	3 days
Filgrastim	and . v ., s . c .	5 μg / kg	24 hours
Molgramostim	and . c .	250 μg / m2 –	24 hours

ANTIAGGREGATION DRUGS

In the arteries, where the blood flow is very fast, white thrombi formed only from aggregated platelets. Thrombi usually occur in places where the atheromatous plaque ruptures, i.e. where the endothelium bursts and the intima is exposed. Platelet aggregation is helped and accelerated by thromboxane A_2 and adenosine diphosphate (ADP), while cyclic adenosine monophosphate (cAMP) slows it down. All these substances are products of platelets themselves. The act of aggregation itself takes place by binding one end of fibrinogen to glycoprotein IIb / IIIa receptors on platelets, and the other end to von Willebrand factor in the exposed intima of the blood vessel.

Platelet aggregation can be reduced by a drug that inhibits the synthesis of prostaglandins in platelets (acetyl-salicylic acid), a drug that increases the concentration of cAMP in platelets (dipyridamole), a drug that blocks receptors for A DP (thienopyridines [ticlopidine, prasugrel and clopidogrel] and ticagrelor) or drugs that bind to IIb / IIIa receptors on platelets and inactivate them (abciximab, eptifibatide and tirofiban).

These drugs are primarily used prophylactically, to prevent thrombosis of coronary arteries (prevention of myocardial infarction) and cerebral arteries (prevention of brain infarction). They also prevent thrombosis after percutaneous interventions on coronary arteries.

Acetylsalicylic acid exhibits an antiplatelet effect only in small doses (100 mg /day or 300 mg every third day) because larger doses also inhibit the formation of endothelial prostaglandins, prostacyclin, (PG I) which otherwise has an anti-aggregation and vasodilator effect.

The effectiveness 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. That is why ***ticlopidine*** is usually used in patients who cannot tolerate aspirin (hypersensitivity, bronchial asthma, etc.), in a dose of 250 mg /12 hours, orally. Today, ticlopidine is used very often to prevent thrombosis in patients who have had a coronary stent implanted.

Clopidogrel and ***prasugrel*** also inhibit the binding of A DP to receptors on platelets, namely to the $P\ 2\ Y_{12}$ receptor type. Both of these drugs can be given in combination with aspirin in patients who have an acute coronary syndrome (consisting of unstable angina pectoris, myocardial infarction with and without ST- elevation), because they lead to a reduction in mortality, repeated myocardial and brain infarctions in such patients. 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 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 creation of the active metabolite is weaker due to genetic reasons, so clopidogrel will not be effective for them. Also, many drugs can affect the metabolism of clopidogrel and thus reduce or increase its effect, which we often cannot control.

Ticagrelor also interferes with the action of A DP on $P\ 2\ Y_{12}$ receptors, but it does not bind to the binding site of A DP, but to some other part of the receptor, with a reversible connection. Ticagrelor, like clopidogrel and prasugrel, is used in patients who have acute coronary syndrome, because it leads to a reduction in mortality, recurrent heart attacks and strokes in such patients. The efficacy of ticagrelor is the same or slightly higher than the efficacy of clopidogrel, and the most significant side effect is bleeding. Tik-agrelor is administered orally.

Dipyridamole is used as an addition to oral anti-coagulant drugs, when they cannot control thrombotic processes in the body by themselves (eg in patients with wash-point valves, in a dose of 75 mg /8 hours, orally). It is also used in combination with acetylsalicylic acid in the secondary prevention of ischemic brain 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 one 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 given 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 (so-called tissue plasminogen-activator). Plasmin found in plasma inactivates alpha2-antiplasmin, while plasmin found in thrombus remains active and breaks down fibrin, i.e. thrombus.

Already formed thrombus can be "broken" by the use of drugs that activate plasminogen and convert it into plasmin. First, la is used ***streptokinase*** (obtained from streptococcus culture extract), primarily for the treatment of fresh myocardial infarction (in the first 12 hours), fresh pulmonary embolism and deep vein thrombosis. Streptokinase acts indirectly: it forms a complex with plasminogen, whereby it is activated and converts other plasminogen molecules into plasmin. It is administered slowly intravenously, in the form of c . infusions. The dose of streptokinase for the treatment of myocardial infarction is 1,500,000 IJ , administered in 100 ml of physiological solution that 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 two-phase: in the first phase ($T_{1/2}$ = 12 minutes) the drug is distributed, and in the second ($T_{1/2}$ = 25 minutes) the drug loses its enzymatic activity. Streptokinase is now rarely used, because the risk of allergic reactions after its use, especially repeated, is higher than with other thrombolytics.

Anistreplase is a complex of streptokinase and plasminogen that is inactivated by the addition of anisoyl radicals. When injected into a vein, the anisoyl radical spontaneously lyses and streptokinase activates plasminogen. Since it is inactive at the time of administration, anistreplase can also be administered i.v. injections, relatively quickly.

Urokinase is also fibrinolytic; it is a di-peptide protease that is normally produced in the renal tubule cells. In practice, it is rarely used for thrombolysis, because it equally activates both circulating plasmin and plasmin bound to the thrombus. It is not immunogenic. The half-elimination time of urokinase is about 20 minutes.

A newer fibrinolytic is ***alteplase***, a human tissue plasminogen activator that is produced by recombinant technology (genetic engineering - a gene that carries information for a certain protein is introduced into E. coli, and it then synthesizes that protein in large quantities) . Unlike streptokinase and anistreplase, alteplase is not immunogenic, ie. does not cause allergic reactions. It is believed that alteplase acts selectively on plasminogen bound in the thrombus, so complications are less common. However, rethrombosis is more common with alteplase, probably due to the short half-life (5-10 minutes).

Today, two new variants of human tissue plasminogen activator are used in practice, ***reteplase*** (it has only those parts of the molecule that are required for binding to fibrin and proteolytic action) and ***tenecteplase***. Reteplase works faster and more efficiently than alteplase (it penetrates deeper into the thrombus), and tenecteplase binds more strongly to the fibrin in the thrombus, acts longer than alteplase and can be administered as an intravenous injection. Clinical studies of desmoteplase, which binds more specifically to plasminogen bound in the thrombus, are ongoing.

After the completion of thrombolytic administration, the patient should be given heparin and oral anticoagulants, as this reduces the frequency of re-thrombosis.

The main side effect when using fibrinolytics is bleeding (in the digestive tract or the CNS). It can be suppressed by inhibition of the conversion of plasminogen to plasmin by tranexamic acid or by direct inhibition of plasmin by aprotinin.

Antifibrinolytics

Tranexamic acid and aminocaproic acid are sometimes used to suppress pathological fibrinolysis (local or systemic) or lysis of the coagulum in case of subarachnoid hemorrhage, so that new bleeding does not occur. The dose of tranexamic acid is 15 mg / kg initially, followed by 30 mg / kg /6 hours orally or 10 mg / kg /6 hours intravenously. Adverse effects tranexamic acid are epileptic seizures, visual disturbances due to damage to the retina, intravascular thrombosis and hypotension.

Aminocaproic acid can also be administered intravenously and orally. Serious adverse effects of aminocaproic acid are intravascular thrombosis, coagulum formation in the urinary tract with hematuria and myopathy with muscle necrosis.

It is of key importance for patient safety to distinguish between pathological fibrinolysis and disseminated intravascular coagulation (DIC) , because the use of antifibrinolytics in DIC worsens the condition and leads to new intravascular thrombosis. In pathological fibrinolysis, the number of platelets is more or less normal, while in DIC it is greatly reduced; in DIC , the protamine paracoagulation test is positive, while in pathological fibrinolysis, the euglobulin lysis test is positive.

BLOOD AND PREPARATIONS OBTAINED BY BLOOD PROCESSING

Applying blood means applying medicine, but at the same time transfusing liquid tissue. That is why the use of blood is much more complicated than the use of other drugs. First of all, the tolerance of the transfused blood should be ensured: it must be antigenically similar to the blood of the recipient. The recipient and donor must have the same blood group in A BO and the Rh

system, and the inter-reaction tests (serum of the recipient with erythrocytes of the donor and serum of the donor with erythrocytes of the recipient) must be negative.

In principle, we use whole blood ("full blood") only when acutely lost blood needs to be compensated (e.g. with severe external or internal bleeding). In all other cases, individual blood elements should be applied 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 in order to avoid introducing into the patient's bloodstream large particles created by aggregation and destruction of erythrocytes during blood stagnation. Only a doctor can administer blood (transfusion)! After introducing the venous catheter and connecting the bottle with blood via the system to it, the doctor should apply about 50 ml of blood, and then stop the transfusion for the next 10 minutes. During that time, the patient is carefully observed, looking for signs of a transfusion reaction due to possible incompatibility of the blood of the recipient and the blood of the donor (pain in the lumbar region, tachycardia, hypotension). Only if these signs are absent, continue with the further administration of blood, at a rate of about 10-20 ml / min .

After collection, whole blood can be stored in a refrigerator at 4 ^{o}C for up to 40 days if it is previously stabilized with a preservative such as CP 2 D -A mixture:

C - citrate (binds calcium ions and thus prevents coagulation)

P - phosphate

2 D - twice the amount of glucose compared to previous condoms

A - adenine.

After a blood transfusion, about 70% of erythrocytes survive for 24 hours. There are few platelets in the whole blood, because they decay already after 24 hours from the beginning of keeping the blood in the refrigerator. Also, whole blood contains as functional only stable coagulation factors (2, 7, 9 and 11).

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 erythrocytes are better used to replace lost blood (with physiological solutions, of course) than whole blood because the excess amount of Na^{+}, K^{+}, lactic acid and citrate is removed with the plasma. Erythromass can be stored in a frozen state ("frozen erythrocytes"), but then it cannot be used in emergency situations.

A special preparation of erythrocytes is represented by **"washed erythrocytes"**. There, the erythromass is washed in 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 antigens of leukocytes and platelets.

Platelet concentrates can be made from blood in a volume of 50 ml. 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 extracted from the blood and used to replace the volume of lost blood. Only if it is fresh (separated immediately after taking blood from the donor) or "freshly frozen" (frozen fresh plasma) does the plasma contain unstable coagulation factors 5 and 8, so it can be used except for volume replacement and for the treatment of coagulation disorders (e.g. .hemophilia). For the treatment of coagulation disorders, specially prepared concentrates of individual coagulation factors or so-called " **cryoprecipitate** " obtained from fresh plasma and containing all coagulation factors.

Albumin concentrates extracted from the blood are used to replace the volume of lost blood as well as to replace lost plasma proteins (eg in burns, nephrotic syndrome, etc.) . These preparations are usually made in concentrations of 5% and 20%. When a total of 25 g of albumin is administered, it represents the osmotic equivalent of 500 ml of plasma. The advantage of albumin compared to plasma is the impossibility of transmitting the hepatitis virus.

With a special procedure, certain coagulation factors can be extracted from the blood and concentrated until a sufficient dose is reached to treat conditions in which these factors are lacking. 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), the so-called **anti-inhibitory coagulation complex**, which contains already activated coagulation factors that are dependent on vitamin K.

Unwanted actions transfused blood and preparations obtained from blood

A hemolytic reaction can occur after transfusion of whole blood or erythromosis if there is incompatibility of A BO, Rh or other antigenic groups between the donor and recipient of blood. This can happen if a mistake is made in the determination of blood groups or an interaction. Hemolysis leads to hemoglobinemia and hemoglobinuria. Symptoms of a hemolytic reaction are: a feeling of heat and pain along the vein into which blood is given, pain in the lumbar region (due to tubule necrosis and reactive inflammatory reaction), facial redness, chest pain, fever, hypotension with tachycardia. Disseminated intravascular coagulation occurs in about 30% of patients.

Febrile reaction. An increase in body temperature may occur after the administration of whole blood, erythromass, plasma, platelets or coagulation factors. It is a relatively common adverse reaction (about 1%).

Allergic reactions can also occur after administration of blood, erythrocytes, plasma, albumin or coagulation factors.

Infections. Syphilis, malaria, hepatitis B , C and E, A IDS , cytomegalovirus and a large number of bacteria that contaminate the taken blood can be transmitted by the use of whole blood, erythromas, platelets or plasma. Today in our country blood is routinely tested for syphilis, hepatitis B and C and A IDS.

Thrombophlebitis at the site of transfusion and **pulmonary edema** follow prolonged transfusions and transfusions of excessively large amounts of these preparations.

COLLOID SOLUTIONS

Colloidal solutions contain particles of high molecular weight that are difficult to leave the bloodstream through the pores in the capillary walls. Thanks 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 the volume of plasma (and thus blood), so colloid solutions are often called "plasma expanders". So far, dextrans, gelatin and etherified starches have been used the most.

Dextrans are polysaccharides that bacteria make 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 bleeding. It interferes with the determination of blood groups, so blood samples should be taken before the administration of dextran. Care should be taken not to overdose (give no more than 500 ml to 1 L in 24 hours) because it can lead to excessive expansion of the plasma and intercellular space (a part of the particles still exits the capillaries), which is manifested by edema of the lungs and other tissues.

Dextran 40 contains particles weighing 40,000 daltons and is made at a concentration of 10% in an isotonic glucose solution. It is primarily used 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 to reduce 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 isotonic sodium chloride solution (0.9%). It is used to replace the volume of lost blood. Like dextrans, gelatin can lead to pulmonary edema and worsening of congestive heart failure.

Etherified starch is a starch composed of 90% amylopectin that is etherified with hydroxyethyl groups. The molecular weight of etherified starch particles ranges from 200,000 to 450,000 daltons. It is made as a 6-10% solution in an isotonic sodium chloride solution. It is used to replace the volume of lost blood. And it can cause pulmonary edema if overdosed (daily maximum up to 1.5 L).

CRYSTALLOID SOLUTIONS

Crystalloid solutions are clear solutions of electrolytes or simple sugars in water. They are used in the form of 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 m O smol / l): 5% glucose, 0.9% sodium chloride, complex physiological solutions (***Ringer's*** solution [Ca^{2+} 2.2 m M/ l , K^+ 4 m M/ l , Na^+ 147 m M/ l , Cl^- 156 m M/ l], ***Hartmann's*** solution, i.e. Ringer's lactate [Ca^{2+} 2 m M/ l , K^+ 5 m M/ l , Na^+ 131 m M/ l , Cl^- 111 m M/ l , HCO_3^- in the form of lactate/ 29 m M/ l] and ***Darrow*** solution [English Darrow , Na^+ 120 mM / l , K^+ 35 mM / l , Cl^- 105 mM / l , lactate 50 mM / l]) and combinations of NaCl with glucose ("glucosal" solution - 1:1 isotonic glucose and isotonic NaCl). Glucose solution is used when there is only a water deficit, while other solutions are used when there is a loss of both water and electrolytes. Derou solution is used when there is acidosis associated with hypokalemia.

For the correction of acidosis, a solution of $NaHCO_3$ in a concentration of 8.4% is used (then 1 ml of the solution contains 1 mM bicarbonate). This solution can be administered as a slow intravenous injection or as an adjunct to an isotonic sodium chloride infusion.

7,4% KCl solution is used to correct hypokalemia (1 ml of this solution contains 1 mM potassium chloride). It is administered 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 the patient cannot take food orally for more than 7 days, parenteral nutrition should be applied. It is administered intravenously, through a central venous catheter, due to the high osmolarity of the solution (if administered through a peripheral vein, thrombophlebitis will inevitably occur).

An adult should be given 2000-2500 k Cal per day with 10-14 g of nitrogen from amino acids (1 g of nitrogen = 6.25 g of protein) in a total of 2-3 L of liquid.

The solutions used should contain all essential and many non-essential l -amino acids. The energy sources to be used in these solutions are glucose and fat emulsions. Glucose should provide 60% of energy, and fat about 30-40% (1 g of glucose = 4 k Cal , 1 g of fat = 9 k Cal). Fat emulsions have the lowest osmolarity and can, apart from the central venous catheter, also be administered through the peripheral vein. Emulsions of fats, apart from their energy value, have another value: they contain essential fatty acids.

Solutions for parenteral nutrition should also contain basic electrolytes (Na^+, Cl^-, K^+, Ca^{2+}), enough phosphate (20-30 mM per day) to ensure glucose phosphorylation, and macro- and micro- elements. Simultaneously with the start of parenteral nutrition, the patient should be given intramuscular doses of vitamin B_{12} and folic acid; other vitamins should be applied 2 times a week.

During the entire period of application of parenteral nutrition, the patient's electrolyte status should be monitored frequently!

Adverse effects of parenteral nutrition are: formation of sludge in the gallbladder, cholestasis and disturbances in the values of liver function tests. After application of fat emulsions, febrile reactions may occur; in addition, fat emulsions interfere with the measurement of the partial pressure of oxygen and carbon dioxide and the concentration of calcium in the blood.

ENTERAL NUTRITION

In the literature the term " enteral diet" was previously imprecisely used only for individual methods of applying special food formulations to patients who are unable to take food in the usual form on their own. Since 2006, when the European society for clinical nutrition and metabolism brought their own guidelines for enteral nutrition, the concept of the enteral nutrition is precisely defined and includes "every form of the nutritional support that includes the application of the special diet made for the special medical purposes". Preparations for enteral nutrition are liquid and are administered by the patient drinking them or through a nasogastric or nasojejunal tube. The largest multicentric clinical study which compared enteral nutrition across nasogastric probes with diet across nasojejunal sonde shew that there was no difference in clinical outcome between groups there including mortality, length hospitalizations, application preparations and frequency pneumonia because of aspirations.

About 25–30 kC al /kg/day should be provided by enteral nutrition. Preparations for enteral nutrition can be divided into ***polymeric*** preparations, which are dominated by macromolecules of proteins, carbohydrates and lipids code which dominate macromolecules proteins , carbohydrates hydrates and lipids , ***digested*** preparations , code which are macromolecules mostly decomposed to peptides , short chains of coal hydrates and fatty acid , i on the ***preparations For special purposes*** , with reduction individual ingredients (e.g. preparation _ with reduced content protein , which se uses the code patients with insufficiency kidneys).

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 amounts, and which 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 (B_1, B_2 complex/riboflavin, nicotinamide, nicotinic acid, folic acid, pantothenic acid/ , B_6, B_{12}, C and H). Vitamins D, K, B_{12} and folic acid are discussed elsewhere in the textbook.

Vitamin A (retinol). Vitamin A exists in nature in 2 forms: retinol (A_1) and 3-dehydroretinol (A_2). Vitamin A can also be synthesized in the human body from provitamin A - plant pigments α, $\beta$and γ-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: aldehyde retinol and retinoic acid. Aldehyde is an integral part of visual purple, rhodopsin, and retinoic acid is a necessary factor for the growth of bones, teeth and epithelium.

Lack of vitamin A (hypovitaminosis A) occurs with deficient nutrition. Symptoms are: night blindness, keratinization of the conjunctiva, clouding of the cornea (Bitot's spots in the beginning, later keratomalacia), defects in the development of the pineal gland and tooth enamel, keratinization of the skin, greater tendency to infections. The daily need for vitamin A is about 2000 IJ .

Vitamin A is used to prevent and treat hypovitaminosis. The therapeutic dose of vitamin A is 25000 I J / 24 hours, orally.

Unwanted effects of vitamin A are manifested when there is an excessive accumulation of this substance in the body (hyper-vitaminosis 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. Trans-retinoic acid (**tretinoin**) is applied locally in the treatment of acne because it accelerates the desquamation of epithelial cells and thus prevents the clogging of the sebaceous gland ducts. And 13-cis-retinoic acid (**isotretinoin**) has the same effect, but is used systemically for the treatment of severe forms of cystic acne (0.5 mg / kg /12 hours, orally). **Etretinate** is obtained by aromatizing the sixth cycle in the retinoic acid molecule. Etretinate has a beneficial effect on patients with psoriasis, especially if they have a pustular form (dose: 3 mg / kg /day, orally). Side effects of isotretinoin and etretinate resemble hypervitaminosis A. In addition, they have a teratogenic effect.

Vitamin E (tocopherol). Vitamin E is found in the sprouts of various seeds, in green leafy vegetables and legumes (beans, peas). Vitamin E is easily oxidized by itself and thus protects against oxidation of other substances - primarily vitamin A and unsaturated

fatty acids in cell membranes. It is thought 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 babies.

The daily need for vitamin E is about 10 mg. Adverse effects of vitamin E have not been described.

Vitamin B 1 (thiamine). Thiamine is a coenzyme in oxidative decarboxylation reactions αof -keto acids, especially pyruvate. It is found in animal liver, meat, black flour and legumes.

Lack of vitamin B 1 can lead to congestive heart failure (so-called wet beriberi) or to neuropathies ("dry beriberi"). Alcoholics may also have a deficiency of vitamin B1, which is manifested by Wernicke's encephalopathy. The daily need for vitamin B 1 is about 1.5 mg.

Vitamin B 1 is used to treat hypovitaminosis B 1. Adverse effects are not known.

Vitamins B 2 complex. Riboflavin is an integral part of flavin-adenine-dinucleotide, a coenzyme that participates in hydrogen transfer in many reactions of cellular respiration and metabolism of amino acids, fatty acids and carbohydrates. It is found in milk, liver, eggs and green leafy vegetables. The daily need for riboflavin is about 1.7 mg.

Riboflavin deficiency is manifested by inflammation of the lips (cheilitis), the appearance of gum disease (cheilosis) and eye problems (photophobia, burning in the eyes, itching). Hypervitaminosis has not been described. Riboflavin is only used to treat hypovitaminosis.

Nicotinamide is an integral part of the coenzymes nicotinamide-adenine-dinucleotide (NAD) and nicotinamide-adenine-dine-nucleotide-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 need 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 (SoA), which is necessary for the metabolism of fatty acids and acetic acid. It is found in almost all foods (that's why it got the name "pan"-totenic acid; pan =everything, everywhere). The daily need for pantothenic acid is 10 mg. The lack of this acid leads to neuropathy, which is manifested by paresthesias on the foot ("burning foot syndrome").

Vitamin B 6 (pyrodoxal) is a coenzyme in transamination and decarboxylation reactions of amino acids. It is found in meat, liver, black flour, green vegetables. The daily need for vitamin B6 is 2 mg.

Vitamin B 6 deficiency causes irritability, convulsions, hypochromic anemia and peripheral neuritis. Seborrhea also occurs. The use of isoniazid leads to a deficiency of vitamin B 6, so it is administered together with isoniazid as a preventive measure. 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 enables 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 need for vitamin C is 60 mg. There is a lot of vitamin C in lemons, oranges, tomatoes, rose hips, and cabbage. Lack of vitamin C is manifested by scurvy (capillary damage, bleeding, gingivitis, tooth loss) and difficult wound healing. Vitamin C should only be used to treat a deficiency. An overdose of vitamin C leads to oxaluria, the formation of calcium - oxalate stones in the kidney and diarrhea.

Biotin (vitamin H) is a coenzyme for carboxylation. It is found a lot in yeast and meat. The daily requirement is 0.25 mg . Vitamin H deficiency is manifested by dermatitis and alopecia. Deficiency occurs with excessive consumption of raw eggs - the protein avidin from the egg white binds vitamin H and hinders its absorption. Hypervitaminosis has not been described.

CALCIUM (Sa)

Calcium is one of the most abundant elements in the human body. It is necessary as an intracellular secondary messenger that enables the vital processes of excitation and contraction in nerve and muscle tissue to proceed smoothly. 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 the increased concentration of calcium in the cytoplasm leads to contraction of microtubules and 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, heart and blood vessels). A decrease in its concentration in the serum leads to hyperexcitability (arrhythmia, tetany), and an increase above normal values to depression of excitable tissues.

Calcium is necessary for the normal construction and growth of bone tissue. In addition, during bone resorption, released minerals neutralize hydrogen ions; bone building, on the contrary, leads to the release of these ions. So, bones are a depot of calcium, 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.

An adult's body has about 1200 g of calcium. Over 99% of all calcium is deposited in bone, mostly as hydroxyapatite. Due to the constantly present remodeling of the skeleton in adults, 250 mg to 1 g of calcium is released daily into the systemic circulation; during the day, that amount accumulates again in the bones.

About 40% to 50% of serum calcium is bound to plasma proteins, mainly albumin. A few percent of serum calcium is bound to organic anions, and about 50% is in free, ionized form. Free, ionized calcium is actually active, so the bound part of serum calcium can be seen as a calcium ***depot.***

Calcium is mainly excreted through stool, bile and urine (99% of filtered calcium is reabsorbed in the tubules).

It is useful to calculate the required doses of calcium to know that 1 mM calcium contains 40 mg of this ion.

Calcium carbonate preparations are mostly 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: stagnation hearts (electromechanical dissociation) , hyperkalemia **,** hypermagnesemia, hyperphosphatemia **,** hypocalcemia **,** prophylaxis osteoporosis and intoxication verapamil**.** The use of calcium is ***contraindicated*** in the following situations: the code the patient which one receive big ones doses cardiotonics and the code which se in EK G - u already see signs toxicity (because serious ventricular arrhythmias may occur) , with existing cardiac arrhythmias (because they may worsen) , with sarcoidosis (because hypercalcemia may occur) , with hypercalcemia and hypercalciuria , with dehydration (due to the occurrence of hypercalcemia), and in a situation where there is hyperparathyroidism or vitamin D poisoning (due to hypercalcemia).

Calcium preparations should be used especially carefully in patients with kidney failure, because hypercalcemia can easily occur in them. In particular, calcium phosphate preparations should not be used because, in addition to hypercalcemia, hyperphosphatemia will also occur.

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 fast administration of calcium preparations intravenously causes vasodilation with hypotension, nausea, cardiac arrhythmias or even cardiac arrest. Therefore, the intravenous injection of calcium must not be administered for less than 20 minutes !
- When hypercalcemia occurs due to calcium overdose , the following symptoms and signs appear: fatigue, weakness , abdominal pain, vomiting, constipation, polyuria, polydipsia, renal calculus, corneal calcification, depression, confusion, shortened Q-T interval and, eventually, cardiac arrest. This syndrome, for the sake of easy memory, can be expressed in popular language: " ***Bones, stones, convulsions and groans!"***
- Nephrolithiasis with prolonged use.
- Prolonged use of alkaline calcium salts (eg calcium carbonate) is associated with the occurrence of "milk-alkali" syndrome (hypercalcemia, alkalosis).

MAGNESIUM (Mg)

Magnesium is a divalent cation (Mg^{++}) that is mostly found intracellularly. As a cofactor, around 300 key enzymes participate in the regulation of a large number of key processes in the body, and above all, it stabilizes the cell membranes of excitable tissues (nerve and muscle). As a medicine, magnesium is administered 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 an energy source. 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 nerve and muscle tissue increases because K^+ is not taken into the cells as needed. In addition to increased excitability, magnesium deficiency is associated with increased urinary potassium loss, so hypomagnesemia exacerbates hypokalemia. In clinical practice, it is known that hypokalemia cannot be satisfactorily corrected if magnesium deficiency is not previously corrected.

Due to its stabilizing effect on the membranes of nerve and muscle cells (both smooth and striated), magnesium exhibits ***anticonvulsant, antiarrhythmic and vasodilatory effects***, and in larger doses can lead to ***inhibition of neuromuscular transmission.***

Magnesium oxide in contact with hydrochloric acid of the stomach acts as ***an antacid***, raising the intragastric pH.

Magnesium sulfate, when taken orally, reaches the small intestine in high concentration, so that the intestinal contents suddenly become hyperosmolar. Under the influence of osmosis, water from the intestinal wall passes into the lumen, stretches the

intestine and causes peristaltic contractions that end in defecation. ***The laxative*** effect of magnesium sulfate ("bitter salts") 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).

There are about 25 g of magnesium in the body of an average person. About 99% of this ion is found intracellularly, and the rest is distributed in the extracellular space. The concentration of total magnesium in the serum ranges from 0.65 to 1.05 mM/l (if the concentration is expressed in milliequivalents, it is twice the amount, because the magnesium ion has two valences). About 50% of the total magnesium in the serum is in the free (ionized) state, which is actually physiologically active.

Magnesium is not metabolized, it passes through the placenta and enters the milk. It is excreted primarily through the kidneys, and to a lesser extent through sweat and intestinal secretions.

Magnesium preparations are indicated in the following conditions: hypomagnesemia, arrhythmias caused by cardiotonic chemical glycosides, chamber tachycardia '' torsades des pointes '', treatment and prevention occurrences of the new convulsions in eclampsia, constipation, bowels preparation For x-ray recording with contrast, status asthmatic, premature childbirth, stall heart and prevention of arrhythmias after the installation of a coronary bypass.

Dosage

For proper dosing, it is useful to know that 1 mM of magnesium has 24 mg of magnesium. All doses listed are for an adult, unless otherwise stated. Different magnesium salts contain the following amount of elemental magnesium :

Table 25. Magnesium compounds

Magnesium salt	1 g contains elemental magnesium:	1 g contains elemental magnesium:
$MgCl_2$	120 mg	4.9 m M
Magnesium gluconate	54 mg	2.2 m M
Magnesium lactate	120 mg	4.9 m M
MgO	603 mg	24.8 m M
$MgSO_4$	99 mg	4.05 m M

The use of magnesium is contraindicated in: patients with AV block, because the block may worsen, hypermagnesemia and dehydration.

Magnesium should be dosed carefully in case of kidney failure, because hypermagnesemia may occur due to reduced excretion. When magnesium is administered parenterally during pregnancy for a period longer than 4 weeks, it is possible that bone anomalies and congenital rickets will occur. Administration of magnesium parenterally immediately before delivery can lead to hypermagnesemia in the newborn, which is manifested by hypotonia and depression of the central nervous system.

Magnesium is excreted in the mother's milk in concentrations twice as high as in the serum, so breastfeeding is not recommended after the administration of large doses of magnesium in the mother.

Magnesium manifests its unwanted effects mainly when hypermagnesemia occurs. Then the following occur: nausea, vomiting, thirst, reddening of the skin with sweating, arrhythmias, drop in blood pressure, drowsiness, depression, confusion, loss of tendon reflexes, muscle weakness, coma and respiratory depression. At extremely high levels of magnesium (>5 mM) in the serum, AV block and then cardiac arrest occur . If administered orally, magnesium may cause abdominal cramps followed by diarrhea.

The dangerous effects of high concentrations of magnesium 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 m M/ l, and in the extracellular fluid 3.5-5 m M/ 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 cell cytoplasm by active transport. Active transport of potassium is supported by glucose and insulin. Through its channels in the cell membrane, K^+ constantly slowly exits the cell and maintains the resting potential of the membrane. When the cell is stimulated (excitation), sodium channels in the membrane open, sodium enters the cell and leads to membrane depolarization. When the channels for sodium are then closed, the channels for potassium are opened, which now massively leaves the cell and leads to repolarization, i.e. return to the potential of peace.

Potassium from the intracellular space is exchanged with hydrogen ions from the extracellular space. Thus, when acidosis occurs, N^+ enters the cells and K^+ leaves them; when alkalosis occurs, N^+ 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, renal hydrogen ion secretion is related to potassium intake. If potassium intake is insufficient, less 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 mainly through the kidneys and very little through the sweat glands. Approximately as much potassium is excreted in 24 hours as was taken in with food. Potassium is excreted in the kidney primarily by tubular secretion, namely in the distal tubule and collecting ducts.

Indications for the use of potassium are hypokalemia and cardiac toxic effects cardiotonic glycoside.

A healthy adult consumes 40-80 mM of potassium daily through food. Potassium should be applied only after determining its concentration in the serum and determining the deficit. Oral preparations should always be given during meals due to their irritating effect on the intestinal mucosa.

Intravenous potassium should only be administered diluted (maximum concentration 40 m M/ l). Before turning on 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 applied, which depends on the concentration of potassium in the patient's plasma. It is usually a dose of about 100 mM /day in adults and about 2 mM / kg /day in children, in the form of 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, insufficiency of the kidney, dehydration, cardiac arrhythmias (because of the possible deterioration), severe ope - kotine (because all the patients are prone to hyperkalemia) or hyperkalemia familiar periodic paralysis.

Side effects of potassium preparations are:

- Ulcerations of the esophagus' wall, of the stomach or of the intestine if the potassium preparation is retained or disintegrated for some reason (slowed mortality or obstruction), so that an extremely high concentration of potassium is reached which damages the mucosa. Ulceration can lead to bleeding or perforation.
- Hyperkalemia (arrhythmias, paresthesias, muscle weakness, confusion, hypotension, A V block and, finally, cardiac arrest).
- Intravenous application of the concentrated potassium solution has an irritating effect on the vein wall and causes pain; this can be alleviated by the administration of lidocaine in an intravenous potassium solution (50 mg per full dose of potassium).

SODIUM BICARBONATE ($NaHCO_3$)

Sodium bicarbonate is an alkaline salt used to counteract acidosis. The normal concentration of bicarbonate in the plasma is 24-30 m M/ l.

Bicarbonates are normal constituents of plasma in which they perform a buffering role. When bicarbonates are taken orally, they neutralize the acid in the stomach, and the excess bicarbonate is then completely absorbed in the intestines. If there is excess bicarbonate in the blood, then they are excreted through the kidneys, alkalinizing the urine. In the kidney, bicarbonate ions are filtered and then reabsorbed in the proximal tubule.

Indications for the use of bicarbonate are: metabolic acidoz, stagnation of the heart, the need to alkalinize the urine in the framework of forced alkaline diuresis and hyperkalemia.

An 8.4% solution of sodium bicarbonate (1 mM/ml) is used for intravenous administration in adults, and a 4.2% solution (0.5 mM/ml) in children. If sodium bicarbonate is given as an intravenous injection, the rate of administration must not exceed 10 mM/min in children. If given as an infusion, it can be diluted in saline or 5% glucose, and must not be administered faster than 1 mM/kg/hour.

PHARMACOLOGY OF THE RESPIRATORY TRACT

TREATMENT OF BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE LUNG DISEASE

The word asthma is of Greek origin, and means "difficult breathing". At the root 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 mentioned 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 the connection between exposure to an allergen and the occurrence of an attack is established in a patient with asthma, we speak of "external asthma", and if the allergic etiology is not clear, we speak of "internal asthma". A person with bronchial asthma has periods of improvement and worsening. The goal of treating bronchial asthma is to prevent the occurrence of attacks (prevention), and to stop attacks that have already occurred. About 5-6% of children and younger people have bronchial asthma.

Chronic obstructive pulmonary disease (COPD) is a disease of the respiratory tract characterized by permanently reduced airflow and an excessive chronic inflammatory response to harmful particles and gases. In patients, exacerbations and remissions alternate. COPD occurs in elderly 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 β_2- receptor agonists, muscarinic receptor blockers, phosphodiesterase blockers, leukotriene receptor blockers, and mast cell stabilizers. Corticosteroids are used as anti-inflammatory drugs.

Long-acting receptor $_2$ agonists β, inhaled corticosteroids, phosphodiesterase blockers and inhaled muscarinic receptor blockers are used to treat COPD.

Agonists of β_2 receptors with a short duration of action can be selective or non-selective; selective (salbutamol, terbutaline, fenoterol, bitolterol) activate significantly more β_2 receptors than β_1 receptor, while non-selective (isoprenaline, orciprenaline, adrenaline) equally activate both β_2 and β_1 receptors. Adrenaline also activates αreceptors.

Selective β_2 receptor agonists are administered by inhalation or orally. The inhalation route of administration is preferable, and should be used whenever possible, because the side effects of drugs are much less pronounced then.

METHOD OF ADMINISTRATION OF DRUGS BY INHALATION

If the patient who needs to use inhalation therapy is a person without reduced physical and intellectual abilities, he can be prescribed medicine in **an inhaler with a measured dose**. With such an inhaler, with one push of the thumb, a precisely determined dose of the drug is released into the air in the form of an aerosol or dry powder, which the patient should inhale using the appropriate technique (the inhaler is held to the lips, the patient simultaneously activates the inhaler with the thumb and inhales air, and then hold the inhaled air for 10 seconds).

If the patient is unable to use a metered-dose inhaler (children, the elderly, retarded persons), the drug is administered through a **nebulizer** (a dose of the drug is introduced into the nebulizer, and an aerosol is created that the patient inhales through a mask, without a special breathing technique) or **a plastic chamber** is placed on the metered-dose inhaler from which the patient inhales the medicine through a mask, without any special technique (after the metered-dose inhaler is activated, the medicine reaches the plastic chamber).

Adrenaline is administered subcutaneously. The effect reaches its maximum after 5-15 minutes, and lasts up to 4 hours.

All short-acting β_2 receptor agonists have unwanted effects due to the activation of β_1 and β_2 receptors in other tissues and organs: hand tremors, palpitations, increased blood pressure, arrhythmias, nervousness. These side effects are also present with the use of selective β_2 agonists, but to a lesser extent, not with non-selective drugs. When using these drugs, one should be especially careful in patients with coronary disease. Due to strong stimulation of the heart muscle and increased consumption of oxygen in it, an attack of angina pectoris and even a myocardial infarction may occur.

Of **the phosphodiesterase blockers in the treatment of bronchial asthma, *theophylline*** is used the most. 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 vegetative nervous system and stimulation of the heart. In addition to causing bronchodilation, theophylline reduces respiratory muscle fatigue and has a certain anti-inflammatory effect. Theophylline is used to stop an asthma attack, to treat exacerbations of

chronic obstructive pulmonary syndrome, and to treat pulmonary edema. It is used as a complex with ethylene-diamine, 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 control the concentration of theophylline in the blood of patients receiving it, because the dose of the drug can be precisely adjusted based on the measured values. You should be especially careful in patients with heart failure, because the metabolism of theophylline is additionally slowed down in them.

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 administration of large doses, convulsions are possible. Theophylline has a stimulating effect on the heart, so arrhythmias can occur. Hypotension occurs due to vasodilatation of blood vessels in the extremities. In order to avoid unwanted 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. longer than 20 minutes.

Theophylline should not be used together with zileuton (leukotriene synthesis blocker), because zileuton inhibits the metabolism of theophylline.

While theophylline is a non-selective blocker of phosphodiesterase, the ***roflumilast as a selective type 4 blocker of phosphodiesterase has recently been used*** to treat a severe form of COPD. Roflumilast is not a bronchodilator, but works by reducing inflammation in the respiratory tract. It is administered orally, and can be combined with other drugs for COPD, except theophylline. Its effect is primarily reflected in the reduction of the number of exacerbations during the year. It is metabolized in the liver via cytochrome P 450. It can cause depression and suicidal tendencies in predisposed patients, as well as weight loss.

Blockers of muscarinic receptors reduce the action of parasympathetic fibers on the bronchial tree, leading to bronchodilation and decreased mucus secretion. The muscarinic receptor blocker ***ipratropium bromide*** can be used to treat asthma attacks, but is less effective than the β_2 agonists. Its true place is in healing COPD and chronic bronchitis accompanied by bronchospasm. As a quaternary ammonium compound, it does not pass through cell membranes, so it is only administered 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 in the form of inhalation. ***Tiotropium*** causes longer-lasting bronchodilation than ipratropium, because it remains bound to M3 receptors longer (up to 36 hours). Bronchodilation after the application of tiotropium lasts for 24 hours, which makes it possible to use it once a day. Tiotropium is used to prevent exacerbation of chronic obstructive pulmonary disease lung diseases, while ipratropium is used to treat exacerbations. Similar to tiotropium are ***aclidinium*** and ***glycopyrronium***, the long-acting blockers of muscarinic receptors 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.

Medicines that affect the functioning of leukotrienes are used only to prevent asthma attacks, always together with at least one medicine from other groups (eg with long-acting beta-agonists and with corticosteroids. Montelukast is a medicine with an attractive **mechanism** of action: it blocks receptors for cysteinyl leukotrienes (C_4, D_4, E_4), substances released by mast cells and considered to contribute to inflammation and bronchoconstriction in asthma. Montelukast is currently only used in the prevention of asthma, in patients who respond poorly to conventional preparations. Its effectiveness is not greater than the effectiveness of beclomethasone. It is taken orally, in one evening dose. Side effects cause headache and abdominal pain. In addition to montelukast, **zafirlukast** is also used as a leukotriene receptor blocker. Both drugs are now indicated for the treatment of asthma caused by It has recently been discovered that leukotriene receptor antagonists can also cause unwanted Churg-Strauss syndrome, which consists of asthma, rhinitis, sinusitis, eosinophilia and vasculitis.

Zileuton inhibits the enzyme 5-lipoxygenase, which converts arachidonic acid into leukotrienes; this reduces the synthesis of not only cysteinyl leukotriene, but also leukotriene B_4.

Zileuton, montelukast and zafirlukast are administered orally. Zileuton causes dyspepsia, and in a small number of patients it leads to an increase in the level of transaminases in the serum. While zileuton increases the concentration of theophylline in the serum (because it inhibits its metabolism), zafirlukast decreases the concentration of theophylline and increases the concentration of warfarin.

Asthmatic attacks can be successfully prevented by using **substances that prevent the release of inflammatory mediators** from mast cells, leukocytes and other cells. These are cromolyn (cromoglycate- N a) and nedocromil. Cromolyn and nedocromil are administered only by inhalation. Less than 1% of substances administered in this way are absorbed into the systemic circulation. Their side effects are rare and mild: nausea, mild pain in the stomach, weak pains in the joints, swelling of the parotid glands, dry cough.

Cromolyn and nedocromil help quickly and effectively in asthma on exertion, while in "external" asthma it takes several weeks to show their full effect.

Corticosteroids are indispensable both for stopping and preventing attacks of bronchial asthma. They are always combined with some of the drugs from other groups. Corticosteroids are used in the form of inhalation (beclomethasone, budesonide, fluticasone) to prevent attacks, and systemic (methylprednisolone, prednisone) to stop attacks. Corticosteroids reduce the inflammation of the airways and thus eliminate the symptoms of asthma. They are very efficient. If they are used systemically for a longer period of time to prevent asthma attacks (several months), significant side effects occur: they can slow down growth in children and cause osteoporosis in adults; peptic ulcer may occur; cataracts may occur in the eye; iatrogenic Cushing's syndrome occurs.

Longer use of corticosteroids should be done by inhalation, because then the side effects are less frequent and less serious; mainly come down to candidiasis of the oral cavity and hoarseness. By rinsing the oral cavity and pharynx with water after each application of the aerosol, even these side effects can be prevented. Only if inhalation administration is not possible (eg mental retardation) should corticosteroids be administered systemically (eg prednisone orally).

If asthmatic attacks cannot be successfully prevented by chronic use of inhaled corticosteroids, then additional improvement is achieved by **the simultaneous use of β_2 -agonists with prolonged action** (salmeterol, formoterol, indacaterol). Combined preparations of corticosteroids and long-acting beta 2 receptor agonists are administered twice a day in the form of inhalation. Their use is contraindicated in an asthma attack itself, because their effect begins slowly (after about an hour), and some constituents from the preparation can provoke paradoxical bronchoconstriction.

Inhaled **salmeterol and formoterol act for more than 12 hours.** and **indacaterol** for even 24 hours, thanks to its liposolubility (retained in cell membranes). They can only be used in the prevention of bronchial asthma attacks, and ***in combination*** with corticosteroids. Self-administration of long-acting β_2 -agonists is associated with worsening of the underlying disease: bronchodilation helps for a while, but as inflammation of the bronchial tree progresses, loss of disease control with β_2 -agonists inevitably occurs.

For severe forms of asthma that have an allergic etiology, i.e. belong to "external" asthma, **biological drugs have been developed** that neutralize certain mediators of inflammation and thus reduce the swelling of the airways. **Benralizumab** binds to the receptor for interleukin 5 (leading to apoptosis of eosinophils and basophils), **mepolizumab** to interleukin 5 itself, and **dupilumab to the receptor for interleukin 4. In addition to these three monoclonal antibodies, omalizumab** is also used , also a monoclonal antibody that binds to IgE . antibodies. Biological drugs are administered as subcutaneous injections, once every 15 to 30 days, as additional therapy to inhalation. It has been shown that the effectiveness of biological drugs is great, because they significantly reduce the number of asthma attacks; at the same time, they are well tolerated - so far, apart from rare allergic reactions, no serious side effects have been recorded.

Finally, in the treatment of asthma, one should never forget that the patient should primarily take enough fluids, i.e. to be well hydrated, in order to reduce the viscosity of the bronchial secretion and facilitate its expectoration.

Table 26. Doses of drugs used in the treatment of bronchial asthma.

MEDICINE	METHOD OF APPLICATIO N	DOSE	GET IT INTERVAL	INDICATION
Salbutamol	Inhalation	2 breaths	5 o'clock	Stopping asthma attacks
Adrenaline	subcutaneously	0.3 mg	20 minutes	Stopping asthma attacks
Ipratropium bromide	Inhalation	2 breaths	6 o'clock	Stopping asthma attacks
Aminophylline	i.v.	250 mg	-	Stopping asthma attacks
Cromolyn	Inhalation	1 breath	6 o'clock	Prevention of asthma attacks
Methylpredniso lone sodium succinate	and . c .	40 mg	-	Stopping asthma attacks

EXPECTORANTS AND MUCOLITICS

When bronchitis is accompanied by a significant secretion in the lumen of the bronchi, the elimination of that secretion by coughing is of the essential importance for the prevention of bronchopneumonia. Bronchi that close with secretion mean distal atelectasis of lung tissue, i.e. increased susceptibility to infection.

In order for it to be coughed up easily, the secretion should be as thin as possible. Medicines 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 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 (irritation of the gastric mucosa reflexly increases the secretion of water and electrolytes in the bronchial mucosa), and partly by a direct effect 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 ulceration of 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 considerable toxicity, synthetic expectorants such as bromhexine are more commonly used today.

Bromhexine increases the amount of bronchial secretion, which becomes rarer, so it is 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 an increase in the level of aminotransferases in the

blood rarely occur. In addition to bromhexine, its active metabolite, ***ambroxol*** is used as an expectorant. The main side effect of ambroxol is 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 via its SH-group to the toxic metabolite of paracetamol and thus neutralizes its effect on liver cells. Side effects of mucolytics are irritation of the gastrointestinal tract and exacerbation of cystitis. They should not be given to people who have ulcer disease because they can cause bleeding in the gastrointestinal tract. They are also contraindicated in children under 2 years of age.

Ivy extract is also useful in the treatment of bronchitis. Active principle ivy (Latin name : Hedera Helix) is ***alpha - hederin***, which perfect absorbs and penetrates into tissues where prevents non-existent regulation beta -2 receptors. As a result of 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 can often appear in the application of the ivy preparations. The causative agent of this unwanted effect is saponin hederacoside C, which as a surfactant dissolves the protective layer of mucus above the gastric epithelium, exposes it to the irritating effect of hydrochloric acid. The similar unwanted effect appears in all the preparations containing saponins as well as in mucolytic drugs.

Table 27. Doses of expectorants and mucolytics.

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Bromhexine	orally	8 mg	8 hours
Carboxycysteine	orally	375 mg	8 hours
Acetylcysteine	orally	200 mg	8 hours

PULMONARY SURFACTANTS

Pulmonary surfactants are drugs used in the treatment of respiratory distress syndrome in premature infants. ***Beractant*** (surfactant of bovine origin) and ***poractant alfa*** (surfactant of porcine origin) are most commonly used. Although the development of several synthetic surfactants was attempted, which even received marketing authorizations, they were all withdrawn from use due to their lower effectiveness than beractants and poractants. Clinical studies with third-generation synthetic surfactants are currently being conducted, but the outcome is still uncertain. Surfactants are applied by "pouring" into the bronchial tree through an endotracheal tube. When they reach the alveoli, they spread over them, reduce the surface tension and prevent the alveoli from collapsing. The most serious side effect is bleeding in the bronchial tree.

ANTITUSTICS

Antitussives are drugs that suppress a dry, unproductive cough. If the cough is accompanied by expectoration of secretions, the use of antitussives is contraindicated because it leads to retention of secretions, blockage of the bronchi, atelectasis and broncho-pneumonia.

Antitussives can suppress cough by inhibiting the cough center in the brain stem (***central*** antitussives) or by reducing the sensitivity of receptors in the coughogenic zones of the pharynx, larynx and trachea (***peripheral*** antitussives). Central antitussives can be opioids or their derivatives (***codeine, morphine, dextromethorphan, pholcodine***), and they can 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. That is why they are used to suppress the most severe forms of dry cough - in the case of infiltration of tussive 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. Today, non-opioid central antitussives are most often used to suppress milder forms of dry cough. They are administered orally. Care should be taken when these drugs are used in small children, because depression of the respiratory center occurs more easily in them than in adults.

Peripheral antitussives (***prenoxydiazine, pentoxyverine***) do not tend to cause respiratory depression, but are less effective in suppressing cough than central antitussives. A relatively effective and completely harmless antitussive is an extract (macerate) of the root ***of marshmallow*** (Altheae radicis). It contains mucous substances that coat the tussogenic zones and reduce the irritation of the receptors. It is taken in small sips every 5-10 minutes.

A simple syrup in children has also been shown to successfully suppress 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

MEDICINE	METHOD OF APPLICATION	DOSE	DOSE INTERVAL
Pholcodine	Orally	10 mg	8 hours
Codeine	Orally	30 mg	8 hours
Butamirate	Orally	50 mg	12 o'clock

CROUP TREATMENT

Croup is a syndrome of obstruction of the upper respiratory tract accompanied by a characteristic cough that resembles the barking of a dog. Croup includes spasmodic (recurrent) croup, laryngotracheitis (viral croup), laryngo t racheobronchitis and laryngotracheobronchopneumonitis. With the onset of this syndrome, which occurs suddenly, most often at night, it is very important to stay calm procedure with a child. If the child is hypoxic, give heliox (mixture oxygen and helium) or only oxygen. The use of wet air is no longer recommended, because it doesn't reduce the percentage of hospitalizations or the severity of the disease. Regardless of the severity of croup, all children should be given ***dexamethasone***, 0.6 mg / kg (max dose 10 milligrams) in ONE doze orally, if possible, and if not, then intravenously or intramuscularly.

Another treatment option is inhalation of budesonide through a nebulizer. Corticosteroids take about 6 hours to work. The effectiveness of inhaled or systematically administered corticosteroids is very similar, but inhaled ones reduce the number of hospitalizations somewhat more. Along with corticosteroids, in moderate to severe croup, adrenaline is administered through nebulizer: 0.5 ml per kilogram (maximum dose 5 ml) adrenaline 1:1.000. The effect of adrenaline is fully manifested after 30 minutes, and lasts for about 2 hours.

OXYGEN

Oxygen is necessary for every cell for the functioning of the respiratory chain that enables the creation of adenosine triphosphate (ATP) , the main intracellular energy "money". 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 application 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 some 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%.

Apart from the mentioned indication, oxygen is also used as an antidote for carbon monoxide (CO) poisoning.

Oxygen is administered through a mask or nasal cannula, usually in a concentration of up to 28%. Higher concentrations can be used only if the patient is not simultaneously in chronic hypercarbia (the partial pressure of carbon dioxide in the blood is permanently elevated). Hypercarbia often occurs in patients with chronic obstructive syndrome. In such patients, the sensitivity of the respiratory center to SO_2 is reduced, so they breathe only thanks to the chemoreceptors in the carotid and aortic corpuscles that detect the low level of oxygen in the blood. If such a patient were given oxygen in a concentration higher 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 cannula should not exceed 4 liters per minute.

When it comes to carbon monoxide poisoning, oxygen can exceptionally be given in a concentration of 100%, even under elevated pressure (hyperbaric oxygen), but short-term (the half-time of elimination of carbon monoxide when applying 100% oxygen is about 90 minutes).

If oxygen is given in higher doses than recommended for a longer time, it exhibits 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 often end tragically because it does not respond to therapy. That is why it is extremely important that oxygen is administered cautiously, in the recommended doses (concentration up to 28%, flow rate up to 4 l / min).

PHARMACOLOGY OF THE GASTROINTESTINAL TRACT

EMETICS

The act of vomiting requires the coordination of several striated and smooth muscles, which is achieved by the vomiting center in the medulla oblongata. Vomiting occurs in several stages. The process begins ***with nausea***, which is followed 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 you try to inhale, while the larynx is closed. Due to the negative pressure created in the esophagus, the contents of the stomach begin to move 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 affected 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 cerebral ventricle) and 3) information from the vestibular apparatus. Therefore, vomiting can cause irritation of the stomach, the presence of some substances in the blood that activate receptors in the chemoreceptor zone (this zone does not have a blood-brain barrier) and premature stimulation of the vestibular apparatus (for example, during a boat or bus ride). In the chemoreceptor zone and vomiting center there are the following receptors, the stimulation of which causes vomiting: dopamine D_2 receptors, serotonin 5- HT_3 receptors, opioid receptors, muscarinic, nicotinic and histamine H_1 receptors. In the vestibular apparatus, activation of muscarinic and histamine H_1 receptors leads to vomiting.

Vomiting must be induced in case of poisoning, within 1 hour of ingestion. It is best to induce it with syrup of ipecac, a South American plant (Cephaelis ipecacuanha) which contains the alkaloid **emetine in its root and rhizome** . 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, oil poisoning, 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 causes vomiting by acting on the gastric mucosa, but also by direct action on the chemoreceptor zone. However, it is also cardiotoxic, so if vomiting does not occur after the application of ipecac syrup, the doctor must perform a gastric lavage (so that emetine is not absorbed).

In the absence of syrup of ipecac, vomiting can be induced by ingesting a glass of water with a little soapy water or with a large spoonful of table salt dissolved in it. Earlier, vomiting was caused by 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 depressing effect on the respiratory center. Apomorphine works better if the poisoned person drinks two glasses of water beforehand. If we don't have any of the above, vomiting can also be induced mechanically, by irritating the palate and pharynx with the tip of a thin leather strap or a finger (beware of the bite!).

ANTIEMETICS

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.

Medicines that block muscarinic receptors (***scopolamine is most often used***) successfully prevent vomiting caused by stimulation of the vestibular apparatus. They are most effective if applied immediately before departure. Usually, scopolamine is applied in the form of a skin patch ", "because due to its high liposolubility, it is perfectly absorbed through the skin.

Blockers of histamine H_1 receptors (***promethazine, diphenhydramine , dimenhydrinate***) are effective in preventing vomiting caused by stimulation of the vestibular apparatus (while driving, or in Ménière's syndrome), but they are also used to treat vomiting in the first trimester of pregnancy (hyperemesis gravidarum). The reason for this second application lies in many years of experience: so far no safe teratogenic effects of antihistamines have been observed. There is not enough experience with other antiemetics when it comes to their use in pregnancy. However, it should be borne in mind that *only severe forms* of vomiting during labor - at night are treated with antihistamines. In most cases, medication is not necessary .

D_2 receptor blockers have proven to be very effective antiemetics . Although classic neuroleptics (for example prochlorperazine) have a strong antiemetic effect, due to pronounced side effects (extrapyramidal syndrome, hypotension, conduction disorders in the heart, etc.), drugs with a slightly more selective effect are used. These are ***metoclopramide and domperidone*** . _ They are mainly used for the treatment of vomiting as part of gastroenteritis, for the treatment of vomiting after the use of cytostatics and for the suppression of vomiting during childbirth and emergency surgical interventions. In addition to the effect on the chemoreceptor zone and the vomiting center, the mentioned drugs promote gastric emptying (raise the tone of the gastroesophageal junction, relax the pylorus, accelerate 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, there may be an increased release of prolactin and galactorrhea in women. Domperidone does not penetrate the blood-brain barrier.

The newer generation of antiemetics consists of drugs that block 5-NT $_3$ receptors (***ondansetron, tropisetron, granisetron***). They are extremely effective in preventing and treating acute vomiting when using cytostatics. Since the beginning of their application, the tolerability of cytostatic therapy has increased significantly. Side effects of ondansetron include headache and feeling hot. ***Palonosetron*** is one of the newer drugs from this group that has the special property of successfully inhibiting both early and delayed vomiting after the administration of cytostatics, so it is preferred for highly emetogenic cytostatics (eg platinum derivatives). In severe forms of vomiting after the application of cytostatics, patients are given corticosteroids, usually ***dexamethasone , in addition to the already mentioned therapy*** . Dexamethasone is also effective in preventing postoperative vomiting.

A large progress on the field prophylaxis and treatment postoperative vomiting and vomiting after the application of cytostatics represents ***aprepitant***, a blocker of neurokinin NK 1 receptors for substance P. Aprepitant after oral administration has long term action (like palonosetron) so successfully protects from the vomiting for up to 48 hours . When used to prevent vomiting after the administration of cytostatics, it is combined with dexamethasone and some of the 5-NT $_3$ receptor blockers. S others sides not it works proarotmogeno, i does not have some more difficult unwanted effects other than hiccups.

Recently, the use of alkaloids from Indian hemp (Cannabis sattiva), which have been shown to have a strong antiemetic effect (***tetrahydrocannabinol*** and others). The effect was incidentally observed in people who abuse drugs from the mentioned plant (hashish and marijuana). The mechanism of action is not clear, but they have been found to work well in cytostatic-induced vomiting. The use of synthetic tetrahydrocannabinol (preparations called dronabinol and nabilone) is approved for the treatment of emesis induced by cytostatics, but only as a second line, when other antiemetics have proven ineffective.

Tetrahydrocannabinol causes sedation (in about 30% of patients), ataxia, dry mouth, and orthostatic hypotension.

Finally, benzo - diazepines also have a certain antiemetic effect. However, they are used only with other antiemetics , because they are not effective enough and because they cause marked sedation.

HYDROCHLORIC ACID AND DIGESTIVE TRACT ENZYMES

Hydrochloric acid (HCl) is used for the treatment of hypo- and achlorhydria, which accompany atrophy of the gastric mucosa. The lack of acid makes it difficult to digest food because pepsin is inactivated in a weakly acidic environment.

Hydrochloric acid is applied by pouring 1-4 ml of a 10% solution into 200 ml of water, and then drinking the diluted acid through a glass straw (so as not to damage tooth enamel) during and after meals. Solid substances can be used instead of solutions, which only release hydrochloric acid in the stomach. 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 already mentioned 10% solution.

In the case of exocrine pancreatic insufficiency (eg 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 end up in the distal small intestine and colon, causing bloating, cramps and abundant stools. Patients with exocrine pancreatic insufficiency can be helped by the administration of pancreatic enzyme preparations.

There are two types of these preparations:

1. ***ordinary pancreatin***, obtained by extracting from pig pancreas, which usually contains 200-600 I J proteases (trypsin and chymotrypsin), 8000-20000 I J lipase and 9000-22000 I J amylase per capsule;
2. ***Pancrealipase***, a preparation that has more lipase than other enzymes (330 I J protease, 5000 I J lipase and 2900 I J amylase per capsule).

Pancreatic enzyme preparations are given during meals. They are dosed individually, based on improving the appearance and composition of the stool.

Adverse effects of enzymes are perianal erosions (in case of overdose), hyperuricemia and hyperuricosuria (due to greater absorption of purine bases, precursors of uric acid).

In practice, it has proven to be an extremely effective preparation of pancreatic enzymes (which patients tolerate very well), a medicine in the form of gastro-resistant granules, under the trade name Creon. These specially made granules break down only in the small intestine, which prevents acid from the stomach from denaturing and inactivating enzymes.

ANTI-ULC THERAPY

Peptic ulcer of the duodenum is a consequence of the hypersecretion of HCl in the stomach and the arrival of an excessive amount of this acid in the bulb of the duodenum. Peptic ulcer of the stomach is caused by reflux of bile from the duodenum and damage to the protective mucosal barrier, so acid from the stomach lumen can penetrate the submucosal layer and damage it. When treating duodenal ulcers, the goal is to reduce acid secretion; when it comes to the treatment of stomach ulcers, the goal is to reduce acid secretion and increase the resistance of the mucosal barrier. In addition, the presence of Helicobacter favors the formation of ulcers pylori , a gram negative bacillus, in the lumen of the stomach and duodenum. If the presence of Helicobacter pylori is detected in a patient, today the prevailing opinion is that eradication therapy should be applied immediately.

HCl is secreted from the parietal cells of the gastric mucosa, by the action of the potassium-hydrogen pump ("proton pump"), which expels the hydrogen ion into the lumen (N^+) and inserts the potassium ion (K^+) into the cytoplasm. Since K^+ passively returns to the

lumen, chlorine ion (Cl^-) follows it . There are N_2 histamine receptors on the parietal cells, the stimulation of which increases acid secretion. On the other hand, the release of histamine from the mast cells of the gastric mucosa is regulated by acetylcholine and gastrin. Through their receptors, both substances increase the release of histamine, and thus the secretion of acid.

$_{2\ receptor}$ 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 Collinger-Ellison syndrome (multiple ulcers due to gastrin-secreting pancreatic tumors). These drugs (especially cimetidine) interfere with the synthesis of sex hormones (impotence, galactorrhea, gynecomastia may occur) and slow down the metabolism of many drugs on the microsomal system of the liver. They are administered both orally and parenterally. While the effect of ***cimetidine and ranitidine*** lasts about 6 hours, ***famotidine and nizatidine*** work longer, 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 a gastric ulcer, therapy can only be started after a gastroscopic biopsy of the ulcer has been performed and cancer has been ruled out by a histological examination. Ulcers refractory to the use of only N_2 blockers often respond well if the selective blocker of M_1 muscarinic receptors - pirenzepine - is added to these drugs.

An unfavorable feature of N2 receptor blockers is the appearance ***of tolerance*** after prolonged use.

HCl secretion can be completely eliminated by using **a proton pump blocker**. Omeprazole, pantoprazole, and esomeprazole are used to treat refractory ulcers that do not respond to $_{N2\ receptor}$ blockers and Colinger-Ellison syndrome. These drugs irreversibly inhibit the proton pump, so it is enough to apply them in just one daily dose. So far, no serious side effects of these drugs have been observed, but studies on mice have shown an increased frequency of gastrinomas in the antrum of the stomach. The most common mild side effect is headache (in 8% of patients); in addition to the headache, diarrhea may occur. Because they are metabolized in the liver to cytochromes, proton pump blockers often interact with other medications that patients are taking at the same time.

Recently, new drugs have emerged that inhibit the proton pump in a different way, competing competitively 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 . In the canaliculi of the parietal cells, they quickly receive protons, because they are weak bases, and then from the luminal side they inhibit the potassium binding site. Only one drug from this group, **vonoprazan ,** is currently in use in Japan. Vonoprazan is metabolized only by cytochrome 3S4, but has a lower potential for interactions with other drugs than proton pump inhibitors.

The acidity of gastric juice can be reduced by using ***antacids*** that directly neutralize HCl . The best effects were 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 regularly if the pH rises to 7 or more). 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 H_2 -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 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 Al^{3+} ^{constipation} and hypophosphatemia (because aluminum binds phosphates from the intestinal lumen and prevents their absorption). The use of antacids should be avoided in people with impaired renal function because hyper-magnesemia or aluminum accumulation may occur. Antacids should not be used at the same time as other medicines, as they can interfere with their absorption.

Helicobacter can be isolated from the antrum and duodenum pylori. They should also be given an antibiotic to which this bacterium is sensitive. In addition to antibiotics, the bismuth-subsalicylate preparation also has a favorable effect on Helicobacter; that's why it is often combined with antibiotics (don't forget to warn patients that bismuth colors the stool black /except for colloidal bismuth preparations/). Eradication of Helicobacter is almost always followed by ulcer healing.

In order to Helicobacter pylori has been safely eliminated, it is necessary to simultaneously apply drugs that reduce acid secretion (some of the proton pump inhibitors) and antibiotics. Today, the therapy of first choice is the so-called triple therapy, which lasts 7 days. The therapy is called ”triple therapy ”because three drugs are used: a protein pump inhibitor, e.g. pantoprazole (40 mg , twice a day), amoxicillin (1 g /12 hours) and clarithromycin (500 mg /12 hours) or metronidazole (400 mg /12 hours). The effect of this therapy is the eradication of Helicobacter pylori in 90% of patients. After those 7 days, the use of proton pump inhibitors (or H_2 blockers) is continued only if the ulcer has been complicated by bleeding or perforation.

In the event that the patient did not respond to ”the triple therapy ”, so that he still has H. pylori, a two-week quadruple therapy ”is applied ”: tripotassium dicitrate bismuth-tat + proton pump inhibitor + two antibiotics. This treatment leads to healing in almost all patients.

For the treatment of stomach ulcers, a preparation made of sucrose and aluminum (***sucralfate***) can be used as a supplement, which covers the mucous membrane of the stomach and the bottom of the ulcer, 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, so it is never combined with other antiulcer drugs. There is a risk of bezoar formation in people who have delayed gastric emptying. In addition to the treatment of stomach ulcers, sucralfate is used for the prevention of stress ulcers in patients in intensive care, and for the treatment of rectal inflammation after irradiation of pelvic tumors (used as an enema).

When administered orally, sucralfate causes constipation.

Acute, superficial ulcers, which occur after the use of acetyl-salicylic acid and other non-steroidal anti-inflammatory drugs, are a special entity. Due to the inhibition of prostaglandin E synthesis, the normal blood flow in the mucosa is disturbed and necrosis of

its superficial layer occurs. Now these ulcers can be successfully prevented by oral administration of ***miso-prostol*** (a derivative of Pg E_1). Its side effects include intestinal colic, mild diarrhea and uterine contractions (it is contraindicated in pregnancy).

Table 29. Doses of antiulcer drugs

MEDICINE	METHOD OF APPLICATIO N	DOSE	DOSE INTERVAL
Ranitidine	Orally	150 mg	12 o'clock
	and . c .	50 mg	8 hours
Mg-Al-trisilicate	Orally	500 mg	The tablet is swallowed (oribleta) between meals and before bedtime
Omeprazole	Orally	20 mg	24 hours
Sucralfate	Orally	1 year	1 g between meals and 1 g at bedtime

PROKINETICS

Prokinetics are drugs that accelerate the propulsive motility of the gastrointestinal tract. They are used for the treatment of paralytic ileus and intestinal paresis after surgical interventions on the abdomen, as well as for the treatment of gastroesophageal reflux. Since the parasympathetic nervous system accelerates motility under physiological conditions, most prokinetics act through or mimic that system. The first prokinetics in clinical use were acetylcholinesterase inhibitors, which reduce the breakdown of acetylcholine and thereby enhance and prolong its effect. ***Neostigmine is*** administered parenterally, in a total dose of 2.5 mg , and shows moderate efficacy.

act in two ways: they activate serotonin 5- HT_4 receptors and release acetylcholine from nerve endings in the intestinal wall. ***Cisapride*** is somewhat more effective than neostigmine because, in addition to increasing motility, it promotes fluid absorption from the intestinal lumen by some still unknown mechanism. The most common side effects are pain in the form of colic 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 EC G , sometimes leading 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 occurrence of constipation. It is well tolerated: its most common side effects are headache and diarrhea.

Metoclopramide also has a prokinetic effect, because it releases acetylcholine from cholinergic nerves and sensitizes gastric smooth muscle cells to acetylcholine. Methox-lopramide is used for the treatment of gastroparesis in diabetics, or after surgical interventions. It is also a useful adjunct to the therapy of reflux esophagitis.

It is interesting that the antibiotic **erythromycin** can also accelerate peristalsis of the gastrointestinal tract, because it activates receptors for the gastrointestinal hormone motilin. This action of his lasts a short time, because tachyphylaxis develops after a day or two.

The only drug proven to **prevent** postoperative ileus is ***alvimopan***. In a number of clinical studies, it has been shown that alvimopan, if taken orally on the day of surgery and then postoperatively, can shorten the time until the establishment of gastrointestinal functions (ie until the appearance of flatulence and the beginning of oral intake) by 10 to 28 hours. Alvimopan is selective blocker μ-opioids receptors which one se they find in gastrointestinal the tract , with what eliminates inhibitory influence opioids on the motility .

SPASMOLITICS

Antispasmodics are drugs that reduce the tone of smooth muscles and thus stop spasms accompanied by colic-type 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, oxyphencyclimine** and others. Propantheline is particularly suitable because, in addition to its antimuscarinic effect, it blocks nicotine receptors in the parasympathetic ganglia of the digestive tract. Due to the quaternary nitrogen in its molecule, it does not penetrate into the CNS and does not exhibit unwanted central effects. The dose of scopolamine butyl bromide is 5 mg /8 hours intramuscularly.

Blockers of calcium channels, especially from the group of dihydropyridines, have a spasmolytic effect. **Nifedipine** has shown greater efficacy than muscarinic receptor blockers in clinical studies, so it should be preferred 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 mostly used for the symptomatic treatment of irritable bowel syndrome and diverticular disease.

The main side effects are headache and heartburn.

In any case, colic must be treated causally - by removing the cause of the spasm (for example, removing calculus from the ureter, removing obstruction in the digestive tract, etc.). Spasmolytics are only an auxiliary, symptomatic tool, which should reduce the patient's suffering while the causal therapy takes effect.

CONSTIPATION THERAPY

We can talk about constipation only when the elimination of feces is performed 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). Therefore, constipation should always be treated causally, by educating the patient about proper nutrition and proper habits. The medicines we use for constipation are called laxatives and can be classified into one of the following groups:

1) ***Medicines that increase the volume of intestinal contents.*** The increase in the volume of intestinal content stretches the intestinal wall and causes defecation. First of all, the patient should take enough liquid 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 column contents. There are a large number of cellulose preparations in the world, but in our conditions, the simplest and cheapest is to recommend the patient to take wheat bran, 2-3 heaped large spoons a day, as they stand for 30 minutes in yogurt or milk. It takes 4-5 days from the start of application to regulate the stool. This method of constipation therapy is the best because it does not have any side effects.

2) ***Osmotic laxatives.*** Medicines from this group are not absorbed after oral administration, they remain in the lumen of the intestine, increase the osmolarity of the contents and cause the passage of water from the intestinal wall into 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 wall of the colon is stretched, the mass reflex "is established "and defecation occurs. Of the osmotic lacsanases, 70% sorbitol, lactulose (a synthetic disaccharide that is not digestible), macrogol (polyethylene glycol) and bitter salt (M gSO 4) are most commonly used today. 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 ordinary constipation because they cause spasms and emptying of almost the entire digestive tract. They are mostly used to prepare the intestines for contrast X-ray studies (irrigography, cecography and others), for colonoscopy and to prevent the absorption of poison after poisoning.

Lactulose (a disaccharide made of galactose and fructose) is broken down in the column under the action of bacteria. It produces a large amount of lactic acid, which lowers the pH of the column and suppresses the growth of bacteria. In addition, the osmolarity of the contents increases, so water passes into the intestinal lumen and the defecation reflex is triggered. Lactulose is used for therapy 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 irritants.*** Medicines 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 activate the neurons of the colon wall after oral intake and absorption. It takes about 8 hours after ingestion to show the effect. Some synthetic substances, for example bisacodyl and glycerol, act similarly. Bisacodyl is administered both orally and rectally, and glycerol only rectally, in the form of an enema or suppository. The dose of bisacodyl is 10 mg orally or rectally, in the evening before going to bed.

In the past, castor oil was widely used as a laxative. Under the action of lipase, it releases ricinoleic acid in the small intestine, which stimulates the neurons in the wall of the small and large intestine. Already after 2-3 hours of ingestion, emptying of the small and large intestines occurs, along with cramps and tearing in the abdomen. Because of these side effects, castor oil is rarely used today.

Stimulating laxatives should be used only occasionally and for a short period of time, because chronic use causes damage to the neurons in the intestinal wall and worsens constipation.

4) ***Laxatives that soften the stool.*** Sometimes it is necessary for the stool to be soft and slippery in order to make the act of defecation as easy as possible. Painful anal fissure, thrombosed external hemorrhoid or perineal abscess represent 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 the stool when using paraffin oil: small amounts of stool can slip through the anus and stain the laundry.

Instead of paraffin oil, **detergents** (surfactants) 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 enable soaking and softening of the contents of the columns. 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 colonic lavage solutions*** 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. Loose 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 the most effective way to prepare the colon for surgery today.

ANTI-DIARRHOICS

Acute diarrhea, whether caused by bacteria or viruses, usually ends on its own, as the causative agents are eliminated in the stool. The most important therapy is the replacement of lost water and electrolytes. It can be administered orally (if the patient does not vomit) or by intravenous infusions. A solution of sodium chloride and glucose is administered orally (due to the cotransport of Na + and glucose in the epithelium of the small intestine), gradually, in small doses ("per 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 a day 500 mg , orally).

Diarrhea caused by a non-infectious agent (eg radiation enteritis, malabsorptive and dyspeptic diarrhoea) can be controlled using ***loperamide or diphenoxylate***, drugs from the opioid group. These two substances have practically no central effects, and in the digestive tract they stimulate μ-receptors and inhibit propulsive motility. Difenox-sylate is often combined with atropine, which further reduces propulsive motility with its antimuscarinic effect. The use of these antidiarrheal drugs is contraindicated if there is an infection with invasive bacteria; it reduces the removal of the causative agent and facilitates the transition to the intestinal wall. The dose of loperamide is 2 mg /6 hours orally. Side effects of loper-mid are abdominal pain, dry mouth, nausea and constipation. Diphenoxylate can cause nausea, itching, dizziness, and numbness of the extremities.

Diarrhea caused by ***ulcerative colitis or Crohn's disease*** (ileitis terminalis) is a specific type of diarrhea. These are autoimmune inflammatory diseases of the wall of the colon and small intestine. A good effect is shown by ***5-aminosalicylic acid*** (5-A S A), which most likely does not prevent the synthesis of prostaglandins in the intestinal wall. 5-A S A can be applied as such (**mesalamine**), as a dimer consisting of two molecules of 5-A S A connected by a covalent bond (**olsa-lazine**) or in a chemical connection with the sulfonamide sulfapyridine (**sulfasalazine**). All these preparations are poorly absorbed, so 5-A S A reaches the colon and acts on the inflamed wall where the normal mucosal barrier has been destroyed. Adverse effects of 5-A S A and other preparations from this group are headache, abdominal pain, interference with folic acid absorption (folic acid supplementation 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's syndrome).

The newest preparation of 5-A S A-e is **balsalazide**. When taken orally, they are not absorbed, they reach the colon, and there, under the influence of bacteria, they are 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 an enema. They can lead to disease remission but at the cost of serious side effects. The best effect of all corticosteroid preparations is ***budesonide***, which is about 200 times more potent than cortisol, and after oral administration it has low bioavailability (because it is metabolized very quickly in the liver to inactive products), so it acts mainly on the gastrointestinal tract (they are less pronounced systemic side effects).

In the most severe forms of Crohn's disease, where there are multiple perianal and intra-abdominal fistulas, patients can be given the so-called "biological" therapy. These are actually drugs (usually of a protein nature) produced by living cells, usually grown in vitro, in the so-called cultures. ***Infliximab*** is one such drug. It is a monoclonal antibody (chimeric mouse-human antibody) that neutralizes tumor necrosis factor alpha (TNF) α, thereby reducing inflammation. Infliximab is administered as an intravenous infusion, once or at most three times, with intervals of one month. The drug is very effective, and leads to the closure of fistulas.

During the administration of infliximab, the patient develops fever, chills, chest pain and hypotension. The mentioned phenomena are transitory, but the real danger is the immunosuppressive effect of the drug: resistance to infections decreases 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 that are found on the membranes of many types of leukocytes, and which are necessary for the leukocyte to attach to 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 [T NF α] and blocks its role in the inflammatory process) and ***certolizumab*** (recombinant , a humanized Fab fragment of an antibody against tumor necrosis factor alpha , which is conjugated with polyethylene glycol, which enables subcutaneous administration every 2 weeks). As with the use of infliximab, after these drugs the human immune system is compromised, so there is a risk of serious infections and some malignant diseases.

A special form of diarrhea is the so-called ***postantibiotic diarrhea***. It occurs after long-term use of broad-spectrum antibiotics, which disrupt the balance between bacteria in the colon. **Milder forms** of post-antibiotic diarrhea are treated by stopping further use of antibiotics and taking the so-called probiotics, i.e. preparations containing non-pathogenic bacteria (lactic acid bacteria, bifidobacteria) mainly from beverages obtained by fermenting milk (yogurt, kefir, etc.). Colonization of non-pathogenic bacteria suppresses the pathogenic bacteria that caused diarrhea. **More severe forms** of post-antibiotic diarrhea are caused by 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, metronidazole should be administered **orally immediately.** If the patient is not cured in 7 days, we also administer **oral** vancomycin for 14 days. In resistant cases, when even vancomycin cannot cure the patient, a new antibiotic for oral administration, ***fidaxomicin***, is used, which is also not absorbed, and has a successful effect on Clostridium difficile .

MEDICINES FOR DISSOLUTION OF BILIARY CALCULUS

Biliary calculosis is the result of an increased concentration of cholesterol in the bile and a decreased concentration of bile acids. If calcium is not deposited in the biliary calculi (ie, if the calculi are not visible on the native X-ray of the abdomen), they can be gradually dissolved by the administration of bile acids. When administered orally, ***chenodeoxycholic acid*** or ***ursodeoxycholic*** acid is absorbed in the ileum, reaches the liver through the blood, where it inhibits hydroxymethyl glutaryl - SoA reductase, a key enzyme involved in cholesterol synthesis. Thus, the concentration of cholesterol in the bile decreases, while the concentration of bile acids increases and they gradually dissolve cholesterol from calculus. Unwanted effects of this therapy are flatulence, diarrhea and liver damage. Urso-deoxycholic acid is significantly less toxic to the liver, so it should be preferred in therapy, even though it is more expensive. Bile acids should be taken for 1-2 years (with occasional breaks) in order to completely dissolve a calculus with a diameter of 1 cm . Calculus larger than 1.5 cm in diameter should not be treated in this way because it takes too long to dissolve completely.

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 onset 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 colic.

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 stomach acid is prevented. Alginates are often combined with antacids. They are used to treat milder forms of gastroesophageal reflux. Both dimethicone and alginates are well tolerated.

ANTIMICROBIAL THERAPY

ANTIBIOTICS

Antibiotics are chemical compounds created by living organisms that can, in small concentrations, stop the life processes of microorganisms (bacteria, rickettsia, chlamydia, fungi, protozoa and viruses). They are divided into bacteriostatics (antibiotics that prevent the growth of bacteria, but do not destroy them) and bactericides (antibiotics that kill bacteria).

Table 30. Bactericidal and bacteriostatic antibiotics

BACTERICIDES	BACTERIOSTATICS
Penicillins	Tetracyclines
Cephalosporins	Erythromycin (low concentrations)
Imipenem	Spectinomycin
Aminoglycosides	Lincomycin
Erythromycin (high concentrations) Trimethoprim-sulfamethoxazole combination	Clindamycin
Vancomycin	Sulfonamides
Quinolones	Chloramphenicol

When using antibiotics, certain principles should be followed that are of great importance for a successful treatment outcome: (1) Antibiotics should not be used if they are not necessary; (2) Before starting the administration of antibiotics based on clinical diagnosis, samples of pus, exudates or infected tissues should always be taken and sent to a microbiological laboratory; (3) The drug should be administered in a sufficient dose; (4) Once the therapy has been started, it should not be changed at least before the end of 3 days, as long as it is necessary to observe the first effects of the treatment; (5) Administration of antibiotics should be followed by drainage of purulent collections, excision of devitalized tissues and removal of foreign bodies; (6) When a clinical cure occurs, the therapy should be continued for at least three more days to prevent relapse; (7) The simultaneous use of bactericidal and bacteriostatic antibiotics is contraindicated, because bactericidal antibiotics act only on dividing bacteria, and bacteriostatics actually prevent the division of bacteria.

APPLICATION OF COMBINATION OF ANTIBIOTICS

Whenever possible, in the treatment of patients with infections, we use only one antibiotic, whose spectrum of action is narrow. In this way, we avoid disturbing the balance between the bacteria in the patient's colon and the creation of resistant strains, which can cause a new infection and put the patient's life in danger. Treatment of infections caused by resistant strains is difficult and with an uncertain outcome, because the choice of antibiotics is then greatly reduced. Unfortunately, we are often in a situation where it is necessary to apply broad-spectrum antibiotics, and that in combination.

There are several indications for the use of a combination of antibiotics. Those are:

1. Treatment of mixed bacterial infections. In such cases, two or more antibiotics with different antibacterial spectrum are applied, so that the effect on all causative agents is achieved.
2. Enhancement of the antibacterial effect on a specific causative agent. This can be achieved by combining antibiotics that act synergistically. The combination of penicillin with streptomycin or gentamicin shows exceptional effectiveness in the treatment of infections caused by Enterococcus faecalis or Staphylococcus aureus. Also, penicillins with an extended spectrum of action (or cephalosporins) and aminoglycosides act synergistically against Pseudomonas aeruginosa. The effect of the combination of sulfonamide and trimethoprim (cotrimoxazole, Bactrim ®) is greater than the simple sum of the effects of individually applied sulfonamides, i.e. trimethoprim. Amphotericin B and flucytosine work synergistically in the treatment of fungal infections.
3. Prevention occurrences resistance the code causative agent . _ The probability of resistance to two antibiotics at the same time is incomparably lower than the probability of resistance to each of them separately.
4. Treatment _ _ te sh kih infection the code which causative agent _ it's not poz-nat . The combination of antibiotics provides a broad anti-bacterial "cover" that guarantees a favorable effect on the causative agent.

Antibiotic combinations have their additional downsides. The risk of toxic effects increases, treatment costs increase, and antagonism between the applied antibiotics may occur if one is bacteriostatic and the other bactericidal. A classic example of antagonism is the treatment of pneumococcal meningitis with a combination of penicillin and tetracycline. Such therapy is significantly more unsuccessful than treatment with penicillin alone.

PROphylactic use of antibiotics

We can use antibiotics both for the treatment of already existing infections and for their prophylaxis. The prophylactic use of antibiotics has long been questionable, but recent clinical trials have proven its justification in precisely defined indications. The basic idea in the prophylactic administration of antibiotics is to achieve a bactericidal concentration of antibiotics in the patient's blood at the moment when the penetration of bacteria into the tissues is expected. Exposed to such a high concentration of antibiotics, the relatively few bacteria that have penetrated the tissues will not be able to survive there.

The most important indications for the prophylactic use of antibiotics are:

1. **Preoperative application**
   a. Antibiotics should not be used prophylactically in all surgical procedures, but only in specific situations. They include : all operations involving the installation of foreign material (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 the 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 can be considered.
   c. One of the examples of prophylactic use of antibiotics is preparation for operations on the head and neck with the opening of the oral cavity, pharynx, esophagus, or trachea (operations in maxillofacial and ENT surgery). In patients who are exposed to such an intervention, it should be applied klin damicin 600 mg and . c . 30 minutes before the start of anesthesia, and then another 300 mg and . c . after 12 hours from the start of anesthesia.
2. Application 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 for the preoperative administration of antibiotics: the drug is given intravenously, half an hour to an hour before the intervention, in only one dose.
3. Long-term administration of the depot preparation benzylpenicillin (benzathine-benzylpenicillin) in children who have suffered an attack of rheumatic fever in order to prevent the recurrence of attacks due to colonization of the pharynx by streptococci.
4. Administration of penicillin or erythromycin before tooth extraction or calculus cleaning in people who have had rheumatic endocarditis (to prevent bacteria from the mouth from settling on previously damaged valves).
5. Long-term use of the depot preparation benzylpenicillin (benzathine-benzylpenicillin) in children whose spleen was removed due to traumatic rupture (because they have a high risk of pneumococcal infections).
6. Prophylactic use of isoniazid in unvaccinated persons living in a household with a tuberculosis patient.
7. Prophylactic administration of rifampicin in all members of a closed collective (eg a company of soldiers) if one of them falls ill with meningococcal meningitis.

Apart from these indications, the prophylactic administration of antibiotics is also justified in patients with malnutrition, a defect in the immune system or in patients under steroid, chemotherapy or radio therapy, if a severe form of neutropenia occurs.

The following table shows the most rational choice of antibiotics for infection prophylaxis in certain surgical interventions:

TYPE OF SURGICAL INTERVENTION	PROPHYLAXIS
Cardiovascular surgery: Reconstruction of the abdominal aorta Leg surgeries involving femoral incision Any vascular operation in which a graft or other foreign body is implanted Amputation of the lower limb due to ischemia Heart surgery Installation of permanent pacemakers	Cefazolin 1 g and . c . as a single dose or 1 g /8 hours for 1-2 days OR cefuroxime 1.5 g and . c . as a single dose or 1.5 g /12 hours, a total of 4 doses OR vancomycin 1 g and . c . as a single dose
Gastroduodenal operations	Cefazolin 1 g and . c . as the only dose or 1 g /12 hours for 2-3 days OR cefuroxime 1.5 g and . c . as a single dose or 1.5 g /12 hours, a total of 4 doses
Biliary surgery, including laparoscopic cholecystectomy in high-risk patients	
Colon surgery , including appendectomy Elective surgery	On the day before surgery, the patient should drink 4 liters of polyethylene glycol solution within 2 hours. He only takes liquids that day. At 1:00 p.m., 2:00 p.m. and 10:00 p.m. on the same day, the patient takes 1 g each of neomycin and erythromycin orally.
Colon surgery , including appendectomy Emergency surgery	Cefazolin 2 g and . c . + metronidazole 500 mg and . c . as a single dose
Abdominal hollow organ rupture	Clindamycin 600 mg/6 hours and . c . + gentamicin 1.5 mg/kg/8 hours and . c . during 5 days
Head and neck surgery that involves opening the mucous membrane of the oral cavity or pharynx	Cefazolin 2 g and . c . as a single dose OR clindamycin 600-900 mg and . c . as the only dose + gentamicin 1.5 mg/kg and . c . as a single dose
Neurosurgical operations , clean, without installing implants	Cefazolin 1 g and . c . as a single dose OR vancomycin 1 g and . c . as a single dose
Neurosurgical operations , clean, contaminated (through the sinuses or nasopharynx)	Clindamycin 900 mg and . c . as a single dose OR Cefuroxime 1.5 g and . c . + metronidazole 0.5 g and . c .

Neurosurgical operations , installation of a CSF shunt	Vancomycin 10 mg into the cerebral ventricles + gentamicin 3 mg into the cerebral ventricles
hysterectomy, vaginal or abdominal	Cefazolin 2 g and . c . as a single dose 30 minutes before surgery OR cefuroxime 1.5 g and . c . 30 minutes before surgery
Cesarean section during active labor or premature rupture of membranes	Cefazolin 1 g and . c . as the only dose as soon as the umbilical cord is clamped
Abortion in the second trimester	Cefazolin 1 g and . c . as a single dose
Installation of a hip joint prosthesis , fusion of spinal vertebrae	Cefazolin 1 g and . c . as a single dose or 1 g /8 hours for 1-2 days OR cefuroxime 1.5 g and . c . as a single dose or another 750 mg/8 hours, a total of 3 doses OR vancomycin 1 g and . c . as a single dose
Installation of prostheses of other joints	Cefazolin 2 g and . c . as a single dose OR cefuroxime 1.5 g and . c . as a single dose or another 750 mg/8 hours, a total of 3 doses OR vancomycin 1 g and . c . as a single dose
Open reposition of a closed fracture with internal fixation	Ceftriaxone 2 g and . c . or and . m . as a single dose
Catheter placement for peritoneal dialysis	Vancomycin 1 g as a single dose 12 hours before surgery
Urological operations - prophylaxis is used only if the patient has bacteriuria	Cefazolin 1 g and . c . at 8 o'clock, 3 doses, and then bactrim orally for 10 days
Prostate biopsy, transrectal	Ciprofloxacin 500 mg orally 12 hours before biopsy and 500 mg orally 12 hours after biopsy
Breast surgery	Cefazolin 1 g and . c . as a single dose
Traumatic wound	Cefazolin 1 g g /8 hours and . c . during 5 days

CHOICE OF ANTIBIOTICS

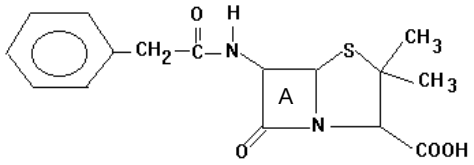
Whenever the patient's condition requires the use of antibiotics without delay, we choose the drug based on our clinical experience, knowing the most common causes of infections in certain locations in the body, and bearing in mind the degree of bacterial resistance in the environment in which we work. Antibiotic therapy determined in this way is called ***empiric*** antibiotic therapy. However, antibiotic treatment must not be started without first taking samples of infected tissues, examining them under a microscope and sowing them on nutrient media. This does not require much time, and it is of great importance for the continuation of the therapy, especially if after a few days it turns out that the applied antibiotic was not effective. When the results of the sensitivity of the bacteria isolated from the tissue of our patient arrive (in jargon known as "antibiogram"), then we can choose the antibiotic to which the isolated bacteria is sensitive. The antibiotic therapy chosen in this way is called " ***targeted*** " therapy.

Advances in medical technology have made it possible to determine a specific causative agent within a few hours, by proving the presence of small amounts of specific DNA for the causative agent in infected tissues. However, even when this is done, the finding must be confirmed by classical seeding 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 act effectively mainly on gram-positive bacteria. In therapeutic concentrations, penicillins are bactericidal. The resistance of a part of bacteria to penicillins is based on the creation of the beta-lactamase enzyme that 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 (phenoxycymethylpenicillin). They are very active against Gram-positive and Gram-negative cocci, but are easily degraded by beta-lactamase.
2. Penicillinase-resistant penicillins (nafcillin, ok sacillin, cloxacillin, dicloxacillin). They are less effective than the first group, but they also work on resistant strains.
3. Penicillins with a wide spectrum of action (ampicillin, amoxicillin, bacampicillin). They also act on gram- negative bacteria, but penicillinase inactivates them.
4. Penicillins with an extended spectrum of action (carbenicillin , ticarcillin, azlocillin, mezlocillin, piperacillin). They also work on Pseudomonas, Proteus, Enterobacter and Klebsiella.

Natural penicillin G (benzylpenicillin) can be found prepared as such in vials, so after dissolution it is administered in the form of 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 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 were 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 attached to one molecule of dibenzyl-ethylene-diamine**, *benzathine-benzylpenicillin*** is formed, which can be applied once every 1-3 weeks, so that penicillin G concentrations are constantly present in the blood above the minimum inhibitory concentrations for sensitive bacteria. There is also a depot preparation ***penicillin G procaine***, where one molecule of penicillin G is attached 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, non-beta-lactamase-producing staphylococci, gonococci, meningococci, 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 the spectrum 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 milder infections caused by beta-lactamase-producing staphylococcus because they are administered orally. Oxacillin and nafcillin are used parenterally to treat more severe infections with this same bacterium.

Ampicillin and amoxicillin, as well as others from the same group, are active against salmonella, shigella, H . influenzae, some strains of E. coli and Proteus. They also work on Streptococcus faecalis. These drugs are acid-resistant, so they can be administered orally. When combined with the beta-lactamase inhibitor ***sulbactam***, ampicillin also acts on the multiresistant bacterium Acinetobacter, one of the most common causes of hospital infections.

Carbenicillin and ticarcillin are also active against Proteus and Pseudomonas. The difference is only in the stronger effect of ticarcillin. They are administered parenterally, often (especially ticarcillin) in combination with the beta-lactamase inhibitor clavulanic acid. Azlocillin is even more active than ticarcillin against Pseudomonas.

Compared to other penicillins, mezlocillin and piperacillin are more active against Pseudomonas and Klebsiella. Piperacillin is also combined with the beta-lactamase inhibitor tazobactam, which reduces the possibility that the causative agents of the infection will be resistant to therapy with a broad spectrum. Today, ***piperacillin with tazobactam is*** one of the few drugs most effective in treating Pseudomonas infections.

Table 31. Daily doses of penicillin preparations
(calculated for a healthy, young man weighing 70 kg) .

MEDICINE	ORAL DOSE	PARENTERAL DOSE
Penicillin G	-	6- 20,000,000 I J i . c .
Procaine-penicillin G	-	600,000 I J/12 hours and . m .
Benzathine - Penicillin G	-	1,200,000 I J i . m .
Penicillin V	500 mg / 6 hours	-
Oxacillin	500 mg / 6 hours	1.5 g / 6 hours and . v ., i . m .
Cloxacillin	250-500 mg / 6 hours	-
Dicloxacillin	250 mg/6 hours	-
Nafcillin	1 year / 6 hours	1 year / 6 hours and . v ., i . m .
Ampicillin	500 mg - 1 g / 6 hours	6-12 g (divided into four doses) and . v ., i . m .
Amoxicillin	250-500 mg / 8 hours	-
Carbenicillin	-	5 g / 6 hours and . v ., i . m .
Ticarcillin	-	200-300 mg /kg and . c .
Azlocillin	-	4 years / 6 hours and . c .
Piperacillin	-	4 years / 6 hours and . c .

Adverse effects of penicillin. The most common side effect is penicillin allergy. It can be any of the 4 types of allergic reactions, but the most common is the first type, an anaphylactic reaction. Ampicillin causes a maculopapular rash in 5% of patients, which does not represent an allergic reaction (especially if it is 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 larger doses of penicillin G are administered intravenously, the appearance of hypernatremia or hyperkalemia is possible, depending on whether the administered preparation is in the form of a sodium or potassium salt.

If an anaphylactic shock occurs after the administration of penicillin, it should be treated first with the administration of adrenaline (0.5 mg and . m . or 0.2 mg and . v ., diluted 1:10 with saline; injection of adrenaline can be repeated after 5 - 10 minutes if there is no improvement), then corticosteroids (eg methyl-prednisolone 80 mg) and antihistamines.

Penicillins are generally not metabolized in the body, and are excreted unchanged through the kidneys, through tubular secretion and filtration. Penicillins penetrate poorly through the intact blood-brain barrier, but their passage increases enough 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 according to the range of activities.

First generation cephalosporins. Antibiotics from this group work on streptococci groups A, B, C and G, on S. viridans , to pneumococcus, to S. aureus and epidermidis , on 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 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 preparations 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 wider spectrum than first-generation cephalosporins, so they also act on: Citrobacter, Enterobacter, a greater number of strains of E. coli, Klebsiella and Proteus mirabilis -a. Except for cefachlor, all other cephalosporins of the second generation are administered only parenterally. Compared to the first generation, drugs from this group are characterized by greater resistance to beta-lactamases. Second generation cephalosporins include: cefachlor, cefamandole, cefoxitin, cefuroxime, cefotetan and others. Cefachlor is very useful for treating otitis media, sinusitis, respiratory infections caused by Haemophylus 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 wider 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 have a weaker effect on staphylococcus than drugs from previous generations. Except for cefpodoxime and cefixime, all are administered only parenterally. Given that they have a weak effect on anaerobic bacteria, if their presence is suspected, 3rd generation cephalosporins should be used in combination with a drug effective against anaerobes (clindamycin, metronidazole). Most of these drugs penetrate well through the blood-brain barrier, so they can be successfully used to treat infections of the central nervous system. This group includes: cefpodoxime, cefixime, cefo-taxime, ceftriaxone, ceftazidime, cefoperazone and moxalactam. Cefotaxime and ceftriaxone are successfully used to treat severe abdominal and pelvic infections, while ceftazidime is now the drug of choice for Pseudomonas infection. aeru - ginosa .

A new cephalosporin that most closely matches the third-generation cephalosporins is ceftolozane, which is only found 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 carbapenem-resistant) , and is also active against anaerobic bacteria and streptococci. It is used in the second line of treatment nosocomial pneumonias, intra-abdominal and urinary infections, usually caused by multiresistant gram-negative bacteria.

Another third-generation cephalosporin has recently been prepared in combination with a beta-lactamase inhibitor, in order to be effective against multiresistant strains of Pseudomonas: **ceftazidime with avibactam** . The advantage of ceftazidime/avibactam over ceftolozane/tazobactam is reflected in the fact that the former also acts on carbapenem-resistant Pseudomonas. It is used in the second line of treatment of hospital infections (pneumonia, peritonitis, complicated urinary infections), usually caused by multiresistant gram-negative bacteria,

4th generation cephalosporins. In recent years, sinte-tisan is the cephalosporin cefepime, which has an even wider spectrum in the gram-negative area than cephalosporins of the 3rd generation, and in terms of its effect on gram-positive bacteria it approaches the cephalosporins of the 1st generation. It works particularly well on P . aeruginosa and S . aureus , so it is used for severe intrahospital infections with resistant bacteria (pneumonia, sepsis, meningitis , osteomyelitis). It penetrates through the hemato-encephalic barrier to the same extent as cephalosporins of the 3rd generation. The use of cefepime should be avoided in patients with severe renal insufficiency, because then encephalopathy may occur .

5th generation cephalosporins. For now, there is only one representative of this group - **ceftaroline** . In addition to acting on gram-negative enterobacteria (except Pseudomonas) and streptococci as third-generation cephalosporins, ceftaroline has an excellent effect on methicillin-resistant staphylococcus aureus and enterococci (E. faecalis). This makes it the antibiotic of choice for complicated skin and subcutaneous tissue infections and for severe pneumonia that started outside the hospital. Ceftaroline is administered as an intravenous infusion, and is mostly excreted unchanged in the urine.

Table 32. Daily doses of some cephalosporins
(calculated for a healthy, young man weighing 70 kg) .

MEDICINE	ORAL DOSE	PARENTERAL DOSE
Cefazolin		1- 1.5 g / 6 hours and . v ., i . m .

Cephalexin	1 year / 6 hours	
Cefuroxime		1.5 g / 8 hours and . v ., i . m .
Cefotaxime		2 years / 12 hours and . v ., i . m .
Ceftriaxone		2 years / 24 hours and . v ., i . m .
Ceftazidime		1 year / 8 hours and . v ., i . m .
Cefepime		2 years / 12 hours and . v ., i . m .

Adverse effects of cephalosporins. The most common side effect of cephalosporin is allergy. It was established that 8 - 20% of patients allergic to penicillins show the same allergic manifestations after the administration of cephalosporins. This is reason enough to avoid the use of cephalosporins in patients allergic to penicillins. Somewhat less often, 2nd and 3rd generation cephalosporins show a nephrotoxic effect. Therefore, their use together with aminoglycosides should be avoided.

Some of the cephalosporins, which have a ring of 4 nitrogen atoms in their molecule (moxalactam, cefoperazone), have specific side effects. They interfere with the synthesis of coagulation factors in the liver, so they can lead to bleeding. In addition, they act similarly to disulfiram on alcohol metabolism: they inhibit aldehyde dehydrogenase and cause unpleasant vasomotor symptoms. Therefore, patients must be warned not to drink alcohol during therapy.

Cephalosporins are also more likely than other antibiotics to cause leukopenia, thrombocytopenia or hemolytic anemia, 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 dori-penem) in their molecule, in addition to the beta-lactam ring, have another cycle made up of only C atoms (hence the carba- in the name). Carbapenems are resistant to most beta-lactamases. They act on 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-sporulating 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 (they normally break down 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 imi-penem is 500 mg /6 hours and . c . 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 and . c . Adverse effects are: nausea and vomiting, measles, thrombocytopenia and liver function disorders. Because 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, there was the development of carbapenem-resistant strains, which today cause a significant percentage of hospital infections. In order to overcome this problem, combinations of carbapenems with beta-lactamase inhibitors were created: **imipenem with cilastatin and relebactam** and **meropenem with vaborbactam** . These antibiotics have proven successful in the treatment of nosocomial pneumonias caused by multiresistant gram-negative bacteria.

Ertapenem differs from meropenem and imipenem in its slower elimination, which allows once-daily dosing. The spectrum of action is similar to that of other carbipenems, but it does not work at all against Pseudomonas and Acinetobacter. It is used for minor infections in the abdomen and pelvis that occurred outside the hospital.

Monobactams. Monobactams also have a beta-lactam ring in their molecule, but apart from it they do not have any other cycle (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 it is very active against almost all enterobacteria. 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 IV or and M

It is interesting that there is no cross-allergy between monobactam 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

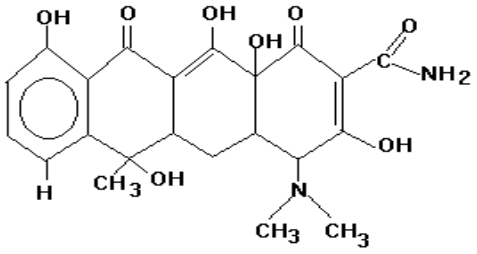
There are several mechanisms by which bacterial cells become resistant to the action of beta-lactam antibiotics: (1) reduced penetration of antibiotics through ***porins*** , openings on the outer lipid membrane of gram-negative bacteria; (2) enhanced expulsion of antibiotics from the periplasm using transport systems in the outer lipid membrane of gram-negative bacteria; (3) modification of penicillin-binding proteins in the cell wall of bacteria, so that their affinity for beta-lactam antibiotics decreases; (4) creation of specific enzymes, the so-called beta-lactamases, which break down the beta-lactam ring of these antibiotics. Certainly the most important mechanism of resistance is the creation of beta-lactamases. There are more than 100 types of them, which are either very specific (so they break down only penicillins or only cephalosporins or only some other beta-lactam antibiotics) or have a wide spectrum, so they break down almost all beta-lactam antibiotics. These latter beta-lactamases are called ”extended-spectrum beta-lactamases ”, and they are produced by the most stubborn bacteria, primarily Klebsiella and Escherichia coli. Infections caused by such bacteria do not respond to cephalosporins and penicillins, and have a very high mortality rate (up to 45%). The only antibiotics that are resistant to the action of extended-release beta-lactamases are carbapenems , ceftolozane with tazobactam , ceftazidime with avibactam and piperacillin with tazobactam, so we rely on them in the most severe infections.

Bacterial resistance to beta-lactam antibiotics can be prevented by a good choice of antibiotics and its application 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 use specific tests to determine the presence of beta-lactamases with an extended spectrum of action; in such cases, carbapenems should be used in maximum doses from the beginning of treatment.

TETRACYCLINES

Tetracyclines inhibit protein synthesis by binding to the 30 S subunit of the ribosome in the bacterial cell. They are bacteriostatic. They are very effective against staphylococcus aureus, pneumococcus and gonococci, but they are not effective against group B and D streptococci. Of the gram-negative bacilli, tetracyclines are sensitive to H . Influenzae, Campylobacter, Brucella , V. _ cholerae , Y ersinia pestis , Francisella tularensis , Yersinia enterocolitica and H . dycrei. Tetracyclines suppress the growth of Actinomyces, Rickettsia, Chlamydia, Mycoplasma and most spirochetes. Today, they are mostly used for the treatment of rickettsial infections (spotted typhus, Q-fever, etc.), infections of the genital organs with chlamydia, and for the treatment of pneumonia caused by mycoplasmas. Also, they are 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 clogging of the openings of the sebaceous glands.



TETRACIKLIN

Tetracyclines differ significantly only in their pharmacokinetic characteristics. On the one hand, there are chlortetracycline, oxytetracycline, demeclocycline and metacycline, which are less well absorbed from the digestive tract (from 30% to 80% of the oral dose) and are mostly excreted via the kidneys. On the other side are ***minocycline and doxycycline***, which are completely absorbed from the digestive tract (100% and 95% of oral doses), and are excreted little (minocycline) or not at all (doxycycline) via the kidneys. Absorption of tetracyclines 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 of them are at least partly excreted through the bile under the enterohepatic circulation. The latter is especially true for doxycycline, which has the longest half-life. Minocycline stands out from other tetracyclines due to its good activity against the multi-resistant hospital pathogen Acinetobacter, so today it is the only antibiotic that can be used orally in the treatment of infections with that bacterium.

Table 33. Daily doses of tetracycline in adults.

MEDICINE	ORAL DOSE	PARENTERAL DOSE
Tetracycline	250-500 mg / 6 hours	500 mg /12 hours and . c .
Doxycycline	100 mg /24 hours	200 mg /24 hours and . c .

The unwanted effects of tetracyclines arise 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 growth of resistant microbial flora in the colon. They lead to photosensitisation, and rarely to toxic effects on the liver and kidneys. They must not be used by pregnant women and children under the age of 8 because they are deposited in the teeth and bones. The teeth acquire a yellowish-brown color, and their enamel is less developed. The mineralization of the bones is disturbed, so they are less resistant to mechanical stress.

Minocycline has a very specific unwanted effect, which causes localized or diffuse hyperpigmentation of the skin or mucous membranes on the places which are exposed to the sun. This hyperpigmentation fades away after the discontinuation of the drug, but it can reappear at the same site if the minocycline is taken again. That kind of change on the skin is also called “fixed measles”.

In practice, it is especially important to know that tetracyclines can reduce a protective effect of the oral contraceptives, so that the conception is possible in spite of regular contraceptive use. Patients should be made aware of this fact, so that they can adjust their sexual activities or use additional forms of contraception.

Tigecycline, a semi-synthetic derivative of minocycline has been recently in clinical use. Tigecycline is administered only intravenously, due to poor absorption after oral administration. It acts on a large number of gram-positive, gram-negative and anaerobic bacteria, *except for proteus and pseudomonas*. Resistance to tigecycline occurs less often than to other tetracyclines, so this antibiotic has found a place in the treatment of polymicrobial abdominal infections, as well as in the treatment of the skin infections. Since it is excreted only through the bile, its dose does not have to be reduced in patients with renal insufficiency. Like other tetracyclines, it causes nausea and vomiting after prolonged use.

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 smaller doses, it has a bacteriostatic effect, and in larger doses, it is bactericidal. It reversibly binds to the 50 S subunit of the ribosome and thus prevents the synthesis of bacterial proteins.

It inhibits the growth and reproduction of pyogenic streptococci, pneumococci, sensitive staphylococci, Cl . perfringens -a, Coryne - bacterium diphtheriae, Listeria monocytogenes. It generally has no effect on gram-negative bacilli, except for H . influenzae. It has an excellent effect on gonococci, and a moderate effect on Borrelia , B. pertussis , P. _ multocida -u, B . fragilis , Campylobacter jejuni , M. scrofulaceum and M. kansasii . Especially important is the good effect of erythromycin on mycoplasmas, chlamydia and Legionella pneumophila.

It is administered orally and parenterally, depending on the severity of the infection. It is excreted in active form in the bile, where it reaches high concentrations. It does not sufficiently penetrate the blood-brain barrier, 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 patients allergic to penicillin who suffer from pneumococcal or streptococcal infections. Also, it is very effective in removing the diphtheria bacillus from the pharynx of germ carriers.

The oral dose of erythromycin is 250-500 mg every 6 hours in a healthy adult.

Adverse effects. Erythromycin estolate can sometimes cause benign cholestatic hepatitis. When using all erythromycin preparations, pain in the epigastrium, abdominal cramps and diarrhea often occur. It is especially difficult for children to tolerate, who usually vomit after oral administration of erythromycin. The basis of these side effects is the activation of the motilin receptor, 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 midekamycin***. These drugs stay longer in the body, so they can be used only once or twice a day. They are better tolerated than erythromycin, because they cause gastrointestinal problems to a lesser extent. Azithromycin stays in the body for a particularly long time, so it is often enough to apply it for only three days, in one daily dose. The spectrum of antibacterial action of newer macrolide antibiotics is similar to the spectrum of action of erythromycin.

Fidaxomicin is a macrolide that isn't absorbed at all from gastrointestinal tract after oral administration. It showed 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 mostly, and other macrolides to a lesser extent, **inhibits the metabolism** of other drugs on cytochrome P450. Therefore, before prescribing one of the macrolides, potential interactions with the drugs that the patient is already taking or will take during the administration of macrolides should be thoroughly 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 occurrence of serious ventricular arrhythmias, especially if he or she simultaneously takes other drugs with the same side effects (some antiarrhythmics, antipsychotics, antidepressants, antibiotics from the group of quinolones, etc.).

KETOLIDES

Ketolides are antibiotics related to macrolides, which are obtained by synthesis from erythromycin. So far, only one ketolide, ***telithromycin, has been put into use***. Telithromycin works by inhibiting the formation of 50 S and 30 S subunits of the ribosome, as well as protein synthesis on the 50 S subunit. Its range of activity includes: staphylococcus that is not resistant to methicillin, many types of streptococcus, Haemophilus influenzae, legionella, Moraxella catarrhalis and some types of chlamydia. Telithromycin has no effect at all on enterobacteria, pseudomonas and acine-tobacter.

Telithromycin is used to treat mild to moderate community-acquired pneumonia, exacerbation of chronic bronchitis, acute sinusitis, and tonsillopharyngitis unresponsive to erythromycin. It is administered orally, once a day.

This antibiotic has a lot of side effects. It can cause cardiac arrhythmias because it prolongs the QT-interval, worsens myasthenia gravis, has a hepatotoxic effect, interferes with the process of accommodation in the eye and inhibits CIP 3A4, which is why it enters into numerous interactions with 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. That is why lincomycin has become an obsolete drug, which is no longer used in practice.

They act in the same way as erthromycin (by binding to the 50 S subunit of the bacterial ribosome and inhibiting protein synthesis), against pneumococci, pyogenic streptococci, S. viridans and staphylococcus. They are extremely active against Bacteroi - des fragilis and other anaerobic bacteria. They inhibit the growth of Actinomyces israelii , Nocardia asteroides and Toxoplasma gondii .

Clindamycin is used 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 and . c . or and . m . It penetrates into all body spaces, except the central nervous system. It penetrates particularly well into bone tissue and abscess walls.

It is mostly 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 one of the aminoglycosides has been shown to be justified whenever a mixed infection with both anaerobes and gram-negative bacteria is suspected. Because it works well on staphylococci and achieves a high concentration in bone tissue, clindamycin is widely used in the therapy of staphylococcal osteomyelitis and arthritis.

Erythromycin mostly, and other macrolides to a lesser extent, inhibits the metabolism of other drugs on cytochrome P450. Staphylococcus resistant to the methicillin (MRSA) should not be treated with clindamycin, because staphylococcus are generally innately resistant to that drug. In the case of innate resistance, strains are usually simultaneously resistant to both clindamycin and macrolide antibiotics. If staphylococcus is isolated before the start of antibiotic therapy, clindamycin should be applied only if the isolated strain is not resistant to macrolides, and if it doesn't 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 fatal in some cases. The cause of colitis is the reproduction in the lumen of the colon of K lostridium difficile, which is resistant to clindamycin. Therefore, as soon as diarrhea appears, the use of clindamycin should be stopped, and then vancomycin or metronidazole should be given to the patient ***orally***.

SPECTINOMYCIN

According to its chemical structure, it is aminocyclitol. It inhibits protein synthesis in gram-negative bacteria by binding to the 30 S 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 only once and . m . injection of 2 g .

The only indication for the use of spectinomycin is uncomplicated gonorrhea, but today it is increasingly suppressed by ceftriaxone in that use as well. Sometimes it causes insomnia, fever, nausea and urticaria.

CHLORAMPHENICOL

Chloramphenicol inhibits protein synthesis in the bacterial cell by reversibly binding to the 50 S subunit of the ribosome. It has a bacteriostatic effect.

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 golden staphylococcus), on rickettsiae and mycoplasmas. It should not be given for chlamydia infections, because it even supports their growth!

It is administered intravenously and orally (in the past it was also administered intramuscularly). It is distributed in all tissues, so it reaches about 70% of the concentration in the blood in the central nervous system. In the liver, it is inactivated by binding with glucuronic acid, and in that form it is excreted through the kidneys. It is interesting that chloramphenicol achieves a higher concentration in the blood 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 are: abdominal typhus; meningitis caused by H. influenzae resistant to ampicillin; meningitis caused by penicillin-resistant meningococcus or streptococcus; brain abscess; severe anaerobic infections; rickettsia infections when we cannot use tetracyclines. The daily dose of chloramphenicol for an adult 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 results in damage to all lineages of the bone marrow. The result is bone marrow aplasia with pancytopenia. The frequency of pancytopenia is not related to the dose of the drug, but it is higher in patients who repeatedly receive chloramphenicol.

If chloramphenicol is administered to a newborn in large doses, gray baby syndrome " occurs. The disease begins around the 4th day from the start of the drug administration. Vomiting, tachypnea, flatulence, cyanosis and rare green stools occur. After 24 hours, the newborn becomes lethargic, his body temperature drops and acidosis occurs. 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 concentration of the drug 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 is more sensitive to them aureus as well as epidermidis. They do not work on anaerobic bacteria.

They are administered only parenterally because they are not absorbed from the digestive tract. They do not pass through the hematoencephalic barrier. They are excreted mostly unchanged through the kidneys.

Aminoglycoside antibiotics are primarily used to treat infections with gram-negative bacteria (urinary tract infections, abdominal infections). Today, streptomycin is used only for the treatment of tuberculosis and diseases caused by Pasteurelle species (tularemia, plague). Due to its high toxicity, neomycin is used only locally (in the form of ointment) and orally for preoperative preparation of the colon. Gentamicin is excreted almost unchanged in the urine, which is why it is suitable for the treatment of urinary infections. Amikacin and tobramycin are reserved for infections with bacteria resistant to other aminoglycosides (eg pseudomonas) because they are more resistant to the enzymes that form the basis of bacterial resistance to this group of antibiotics. All aminoglycosides act synergistically with beta-lactam antibiotics.

Daily doses of some aminoglycosides for an adult are: amikacin 15 mg / kg and . m . , and v .; gentamicin 3 mg / kg and . m . , and v .; streptomycin 14-28 mg / kg and . m .; neomycin 1 g /6 hours orally, for preoperative preparation of the colon. Aminoglycosides should be administered in as few daily doses as possible (preferably in one or two), because then their effect on the cause of 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 drops to an unmeasurable level (due to stimulation of granulocytes). Also, the toxicity of aminoglycosides is lower, if they are administered in fewer daily doses (because the toxic effects depend not ***on the level*** of concentration in the blood, but ***on the length of time*** the concentration of the drug is present in the blood, which has the potential to damage the patient's tissues and organs).

Adverse effects of aminoglycosides are dose-dependent. They accumulate in the peri- and endo-lymph of the inner ear and the vestibular apparatus, leading to progressive destruction of the vestibular and cochlear sensory cells. Patients initially experience tinnitus, nausea, and vomiting, followed by loss of high-frequency tone perception, dizziness, and ataxia.

In addition to ***ototoxicity***, aminoglycosides also have ***nephrotoxic*** properties because they damage the cells of the proximal tubules. This tubule damage is usually reversible. Tobramycin is less nephrotoxic than other aminoglycosides.

Of special importance for anesthesiology is the property of amino-glycosides to act as neuromuscular blockers. If applied immediately before general anesthesia, they can potentiate the effect of neuromuscular blockers and lead to prolonged muscle paralysis and apnea. In such cases, a calcium preparation should be administered intravenously.

SULFONAMIDES

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, they are not affected by sulfonamides.

Sulfonamides inhibit the growth of pyogenic streptococcus, pneumococcus, Haemophilus influenzae, H . Dycrei , Nocardia , Actinomyces and chlamydia. They act as bacteriostatic agents.

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 ***quickly absorbed and quickly 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 for the treatment of diseases of the digestive tube itself. The best-known representative of this group is sulfasalazine. Sulfonamides ***for local application*** (sulfacetamide, mafenide, silver-sulfadiazine) form the third group, while the fourth includes drugs that are ***quickly 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 infections (most often caused by E. coli) respond well to sulfonamides (sulfisoxazole and sulfamethoxazole). Also, they can be used for the prevention of recurrence of rheumatic fever (sulfadiazine) as an alternative in patients who are allergic to penicillin. The use of sulfonamides in the treatment of pyogenic infections is seriously limited by the property of pus to inactivate them due to the high concentration of amino acids and purine bases. Local mafenide or silver-sulfadiazine, in the form of creams, are used to treat burns.

Daily doses of some sulfonamides for 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. Today, only sulfadiazine is used parenterally (intravenously); such application is complicated, because due to 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 that they are contraindicated in children under 12 years of age, at the end of pregnancy and during lactation. Sulfonamides cause many changes on the skin: photosensitization, exfoliative

dermatitis and Stevens-Johnson syndrome (erythema multiforme associated with mucosal ulcerations). Other problems are hematological side effects (agranulocytosis, anemia) and nephrotoxicity due to crystallization of the drug in the tubule lumen (this can be easily prevented by taking enough fluids and alkalinizing the urine).

A special place in therapy is 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, pneumocystis pneumonia, typhoid fever unresponsive to chloramphenicol and ampicillin, and shigellosis. Also, Bactrim can be used for the treatment of respiratory infections and for the treatment of hospital-acquired infections in seriously ill patients with multi-resistant Stenotrophomonas bacteria. 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 given intravenously, in the same dose as orally.

Bactrim ®is contraindicated in pregnancy and lactation.

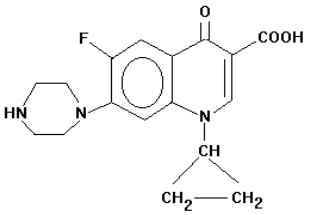
Like sulfonamides, trimethoprim penetrates perfectly into all tissues, including the brain. Most of the ingested drug is eliminated unchanged in the urine.

Adverse 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 alleviated by the use of folinic acid.

QUINOLONES

Quinolones are synthetic antimicrobial drugs with a very broad spectrum of action and the possibility of oral administration. They inhibit DNA gyrase, an enzyme that is necessary for the "supercoiling " of bacterial DNA, ie. for bacterial chromosome formation. In therapeutic concentrations, they have a bactericidal effect.

CIPROFLOKSACIN



Quinolones are usually divided into non-fluorinated (also called quinolones of the 1st generation), which reach sufficient concentration to eliminate bacteria only in the urinary tract, and fluorinated (or quinolones of the 2nd generation), which reach therapeutic concentrations in most tissues. Non-fluorinated quinolones (pipemidine acid, nalidixic acid) are useful or only as uroantiseptics, while fluorinated quinolones (ciprofloxacin, olfloxacin, levofloxacin, moxifloxacin) can be used in the treatment of infections of most tissues and organs. Although it is fluorinated, norfloxacin still does not reach sufficient concentrations in other tissues, so it is used, like quinolones of the 1st generation, for the treatment of urinary infections. The use of non-fluorinated quinolones in practice has stopped, due to the fact that they were used for mild infections, where they could cause potentially severe side effects: inflammation of tendons with possible rupture, neuropathy, depression, taste and smell disorders. Only norfloxacin is still used as a uroantiseptic from this group.

Quinolones have an excellent effect on E. coli, Salmonellae, Shigellae, Enterobacter, Campylobacter and Neisseria. They have a slightly weaker effect on pseudomonas, enterococcus and pneumococcus. Staphylococcus resistant to methicillin reacts well to ciprofloxacin, as well as chlamydia, mycoplasma, brucella, legionella and mycobacteria. However, all quinolones with the exception of moxifloxacin have a very weak 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 along with quinolones.

They are well absorbed from the digestive tract and they penetrate into 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 infections and prostatitis. Soft tissue and bone infections also respond well to these medications. 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 came into use, which achieve significantly higher concentrations in the respiratory tract than other fluoroquinolones. This is why they are more effective than others in the treatment of respiratory infections, so they are called "respiratory quinolones ".

Adverse effects. Fluroquinolones are relatively well tolerated. Rarely, nausea and light headache occur, and sometimes photosensitivity and skin rash. They also have a specific unwanted effect on the tendons of the large muscles of the extremities, especially on the Achilles tendon, which makes them less resistant to stress. If patients are not careful and expose themselves to physical exertion, these tendons may ***rupture due to strong muscle contractions.*** Therefore, it is imperative to warn patients who are prescribed fluoroquinolones to avoid physical exertion while taking these drugs and for a few weeks afterwards.

A special problem is the tendency of fluoroquinolones to prolong the QT-interval and have a proarrhythmogenic effect. Their use should be avoided in persons with myocardial diseases, especially in combination with other proarrhythmogenic drugs (eg with amiodarone）.

They are contraindicated in pregnant women, lactating women and children under the age of 17 because they disturb the normal growth of joint cartilages. They should also not be given to patients with CNS disease because they can cause convulsions. In old people, they can cause a confused state. Sometimes they cause neuropathy, depression and disturbance of the sense of taste and smell.

Unfortunately, resistance to fluoroquinolones is quickly created, even during therapy, especially if the causative agent is Pseudomonas. There is cross-resistance among members of this group of drugs.

POLYMYXIN B AND COLISTIN (POLYMYXIN E)

Polymyxins are peptides in 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. Because they act as detergents, they increase the permeability of bacterial membranes and thus lead to cell lysis. They only work against gram-negative bacteria because only they have an outer lipid membrane around the cell wall.

In our country, colistin (colistimethate) is used as a preparation for intravenous infusion, primarily in hospital conditions 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. More than 80% of the ingested dose of colistin is eliminated through the kidneys, in an unchanged form. It is administered in three doses a day, due to the short half-elimination time.

Colistin is extremely nephrotoxic and neurotoxic (in the central and peripheral nervous system, it can lead to cessation of breathing).

Polymyxins are not absorbed from the digestive tract. Polymyxin B is used only for topical treatment of infections of the skin, visible mucous membranes, eye and ear.

BACITRACIN

Bacitracin is a polypeptide that inhibits the synthesis of the bacterial cell wall. It is active against: most gram- positive bacteria, especially Haemophilus, Treponema pallidum, Actinomyces and Fusobacterium. It is used only locally - for infections of the skin, visible mucous membranes and eyes, because systemic application leads to kidney damage.

Becitracin is often combined with neomycin in preparations for the local use, because neomycin acts on gram-negative bacteria, and on gram-positive bacteria it acts synergistically with bacitracin. Neomycin is an antibiotic from the group of aminoglycosides, which inhibits protein synthesis in the bacterial cell. Bacitracin is not significantly absorbed from the application site, even when the skin or mucous membranes are damaged; neomycin can be more significantly absorbed if it is applied to damaged skin or mucous membrane for a long time, and then it can have an ototoxic and nephrotoxic effect.

GLYCOPEPTIDE ANTIBIOTICS

The group of glycopeptide antibiotics includes vancomycin and teicoplanin. ***Vancomycin*** is a polypeptide antibiotic that inhibits the synthesis of the cell wall of bacteria, but the mechanism is different from that of penicillin. It has a bactericidal effect on gram-positive bacteria and on Clostridium difficulties. Its effect on staphylococci resistance to other antibiotics is especially useful (especially methicillin-resistant staphylococcus) and enterococci.

Neap is absorbed from the digestive tract, so it is administered orally for the treatment of pseudomembranous colitis after the administration of antibiotics (caused by the reproduction of Clostridium difficile; most often this complication occurs after the administration 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 in the form of intravenous infusion.

The main side effects are ototoxicity and nephrotoxicity. During intravenous administration, the dose of vancomycin must be diluted in 500 ml of 5% glucose and given slowly, in the form of 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 appears (the so-called ***red man syndrome***).

Since the toxicity of vancomycin is directly dependent on its concentration in the serum, it is recommended to monitor the concentration of vancomycin during therapy in order to prevent the occurrence of side effects in time.

Teicoplanin works by a similar mechanism as vancomycin. Due to slower elimination, it can be applied only once daily. Also, teicoplanin can be administered *intramuscularly*, which is suitable 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

In the beginning, only the effect of metronidazole on Trichomonas vaginalis, E. hystolitica and G . lamblia was known. It was later discovered that it has a strong antibacterial effect on all anaerobic cocci, on anaerobic gram-negative bacilli (including Bacteroides) and on anaerobic sporulating 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 on animals that it can have a carcinogenic effect, but this has not been proven in humans.

It can be administered both orally and parenterally. It is partly metabolized in the liver and excreted through the kidneys, coloring the urine red-brown.

In addition to being used to treat protozoan infections, metronidazole has found use in severe abdominal and pelvic infections caused by anaerobic bacteria. It is also useful for the treatment of pseudomembranous colitis caused by Cl. difficile. The dose of metronidazole is 500 mg /8 hours orally, and in case of intravenous administration, 1 g is given as an initial dose, to be extended later with 500 mg / 8 hours.

Adverse effects. The most common side effects are headache, nausea, dry mouth and metallic taste. Sometimes it manifests neurotoxic changes, both on the central nervous system (vertigo, rarely convulsions and ataxia) and on 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, as it has teratogenic potential.

Metronidazole enters in interaction with a large number of medicines which are metabolized in the liver, because it inhibits their metabolism and brings to an increased concentration of those medicines in blood (eg carbamazepine, ciclosporin, fluorouracil). That's why when metronidazole is prescribed, the possible interactions with medicines that the patient already takes should be checked (take a look at Summary characteristic medicine).

STREPTOGRAMINA

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 bacterial cells and act bactericidally on Gram-positive bacteria: streptococci and staphylococci, including strains resistant to other antibiotics. On Enterococcus faecium act bacteriostatically, while on Enterococcus faecalis do not work at all.

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 mostly excreted through the bile. They inhibit the enzyme CIP 3A4, so they can slow down the metabolism of other drugs: warfarin, diazepam, astemizole, terfenadine, ciclosporin, etc.

The most common side effect is muscle and joint pain during and immediately after the infusion.

OXAZOLIDINONES

Oxazolidine and 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. 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 methicillin- and vancomycin - resistant staphylococci.

The new oxazolidinone is ***tedizolid***, which inhibits protein synthesis in the bacterial cell. Tedizolid is active against gram-positive bacteria, especially streptococci, staphylococci and enterococci. For now, it is 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 long-term use.

DAPTOMYCIN

Daptomycin is a cyclic lipopeptide, which binds to the bacterial cell membrane and causes depolarization. As a result of depolarization, the synthesis of proteins, DNA and RNA is inhibited, which leads to the death of the bacterium.

Daptomycin acts only on Gram-positive bacteria, primarily staphylococci and streptococci. That is why it is indicated for the treatment of complicated skin and soft tissue infections, right-sided infective endocarditis caused by Staphylococcus aureus bacteria and bacteremia accompanying these two diseases. It is administered as an intravenous infusion, once a day. It is distributed in the extracellular fluid, and only minimally passes through the hematoencephalic barrier.

Daptomycin is not metabolized to a significant extent, and most of it is excreted unchanged in the urine, by the mechanism of glomerular filtration. Unfortunately, daptomycin is a very toxic drug. It often causes muscle pain and an increase in cretin-phosphokinase in the blood, and occasionally myositis, which can progress to rhabdomyolysis. That is why daptomycin should not be used in patients who receive statins at the same time, because the risk of muscle damage is even greater. In addition, liver and kidney function impairment, anemia, prolongation of prothrombin time may occur, and a small number of patients (the exact frequency is unknown) may develop eosinophilic pneumonia.

THERAPY OF TUBERCULOSIS

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 antituberculotics.

Therapy is started with a combination of three or four first-line anti - tuberculotic 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) persons living in a house with a tuberculosis patient; (2) persons who have not been vaccinated, and the tuberculin test has become positive ; (3) persons who are in a state of immunosuppression (AIDS , steroid therapy, etc.). When it comes to **latent** tuberculosis, i.e. there is an infection without symptoms, the use of only isoniazid for 9 months is indicated. It is well resorbed and penetrates into 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 over $_{\text{time by using vitamin B6}}$ with isoniazid (10 mg /day). In addition, isoniazid can cause chemical hepatitis.

Rifampicin blocks RNA synthesis in mycobacteria. It is used for the treatment of tuberculosis in an oral dose of 600 mg, before meals, three times a week. The doctor should warn the patient that rifampicin colors 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 action 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 in a dose of 25 mg / kg /day, orally. It can cause inflammation of the optic nerve, which is first manifested by a color vision disorder. It weakly penetrates the central nervous system.

Pyrazinamide kills tuberculosis bacilli that are found in macrophages (in the acidic environment of their lysosomes). The dose of pi - razinamide 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 me it acts primarily on mycobacteria in the extracellular space and caverns (dose: 15 mg / kg / day i.m. or i.v.) .

The initial treatment of tuberculosis lasts 8 weeks. Four drugs are used: isoniazid, rifampicin, ethambutol and pyrazine - mid. Serum liver enzyme levels should be monitored weekly. After the first 8 weeks, the administration of only two drugs, rifampicin and isoniazid, continues for 4 months. The largest number of patients will be cured with this kind of therapy. For resistant cases they use 2nd- line antituberculosis : (1) parenteral preparations (streptomycin , kanamycin , amikacin or capreomycin), (2) quinolones (moxifloxacin , levofloxacin , gatifloxacin , ciprofloxacin and ofloxacin), and (3) drugs which one se they give oral via and they act bacteriostatic (ethionamide , prothionamide , cycloserine , para - aminosalicylic acid , terizidone). **Kanamycin and amikacin** are aminoglycosides antibiotics, while **capreomycin** is peptide antibiotic which is toxic for internal ear and kidneys. **E thionamide** inhibits synthesis protein in mycobacteria; it penetrates all tissues, metabolizes in the liver to active and inactive metabolites, it is hepatotoxic and it causes neuropathy, the psychotic reactions and encephalopathy, so it applies together with vitamin B 6 and nicotinamide. **Prothionamide** has similar mechanism actions and toxicity like ethionamide. **Steam - aminosalicylic** acid blocks synthesis full 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 analog of d-alanine that is normally incorporated into the cell wall. Cycloserine has excellent penetration into most tissues, including the central nervous system; it is mostly excreted unchanged through the urine, and a smaller part of the dose is metabolized in the liver. The main side effects of cycloserine are on the central nervous system: in larger 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.
These 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 a sterol residue in the membranes of fungal cells, increasing their permeability to ions and small molecules. Water enters the cell of the fungus uncontrollably, it swells and finally sprays. 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 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 passes through the hematoencephalic barrier. Amphotericin B is metabolized in the liver and mostly excreted through the bile. Only 5% of the administered drug dose is excreted as unchanged drug in the urine. The elimination of the drug is slow, two-phase: the half - elimination time 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. c.

Adverse effects of amphotericin B are: pyrexia, azotemia due to toxic effect on kidney tubules and anemia due to inhibition of erythropoietin synthesis in the kidney. Tubular damage is reversible if the drug is stopped in time. Thrombophlebitis usually occurs at the site of infusion of this drug.

In order to reduce the toxicity of amphotericin B, a preparation was made in which the amphotericin molecules are enclosed in small balls of phospholipids: liposomes. Liposomal amphotericin B is significantly more expensive, but side effects are much rarer compared to the use of ordinary 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 clinically used only for the treatment of local candida infections. 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 IJ /8 hours.

Flucytosine

In fungal cells, flucytosine is transformed into 5-fluoro - uracil, which interferes with the synthesis of RNA and DNA (it inhibits the enzyme thymidilate synthase, so there is not enough thymidine, 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 disease recurrence 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. Half-elimination time is 3-5 hours. Flucytosine can lead to bone marrow depression and liver damage, especially in patients with AIDS.

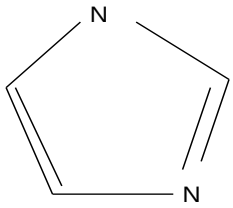
Echinocandins

Caspofungin, micafingin and anidulafungin are representatives 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 (these are usually non-albicans strains), as well as 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 the following may occur rarely : nausea, vomiting, fever, facial flushing, anemia, and liver damage. Unlike imidazole, it interacts with other drugs to a very small extent.

Anidulafungin and micafungin have slightly fewer side effects than caspofungin, and interact even less often with other drugs. Anidulafungin remains in the body longer than the other two echinocandins, and is the only one that is degraded by spontaneous hydrolysis in the bile ducts. Micafungin is the only one approved for use in very young children.

Imidazoles

All compounds from this group contain an imidazole ring in their molecule. Imidazoles interfere with the synthesis of ergosterol necessary for the integrity of the fungal membrane. They are very active against many known pathogenic fungi; in addition, the occurrence of resistance is rare.



Imidazole ring

Due to their high toxicity, some of the imidazoles are applied only locally (clotrimazole, econazole), while others are applied both systemically and locally (ketoconazole, miconazole).

Ketoconazole is administered orally, but its absorption is relatively weak; it does not reach fungicidal concentrations in the serum. A necessary prerequisite for its absorption is the normal acidity of the gastric juice, so that N_2 receptor blockers and antacids can significantly reduce the bioavailability of an oral dose of ketoconazole. It is metabolized almost completely in the liver, and its metabolites are excreted through the bile. Ketoconazole is used for the treatment of non-meningeal blastomycosis, histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, chronic mucocutaneous candidiasis, and widespread forms of dermatophyte infections (trichophytia, epidermophytia, microsporia), but only under the condition that these are milder forms of infection and that the central nervous system is not affected.

Miconazole acts on the same pathogens, but it can only be administered intravenously, because only 10% of the ingested drug is absorbed from the gastrointestinal tract. Miconazole also penetrates the central nervous system poorly. The dose of ketoconazole is 200-400 mg per day, in one 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 the inhibition of the synthesis of steroid hormones, leads to a series of endocrine disorders in about 10% of patients: amenorrhea, gynecomastia, oligospermia, Addison's disease. A small number of patients (1: 12,000) may develop hepatitis. On the other hand, miconazole can cause vomiting or even cardiac arrest if administered rapidly intravenously; therefore, it should be given in an infusion lasting at least 1 hour. Also, miconazole has serious central neurotoxic effects: tremors, confusion, hallucinations.

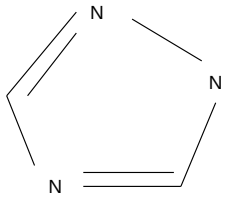
Clotrimazole and econazole are used only topically, for the treatment of skin infections caused by dermatophytes (epidermophytia, trichophytia, microsporia), candida or pityriasis versicolor.

Ketoconazole interacts significantly with many drugs that are metabolized by the same type of cytochrome P 450 in the liver. Thus, rifampicin and isoniazid lower the concentration of ketoconazole in the blood, and ketoconazole increases the concentration of warfarin and sulfonylurea derivatives.

Triazoles

Triazoles (fluconazole, itraconazole, voriconazole, posa-conazole) are closely related to imidazoles. They act by the same mechanism as imidazoles and have a similar spectrum of action. They act well on: 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 an imidazole, they have a triazole ring in their molecule.

Fluconazole penetrates the central nervous system very well, so it is used to treat cryptococcal meningitis and systemic candidiasis. On the other hand, itraconazole barely crosses the blood-brain barrier and is primarily used for sporotrichosis, coccidioidomycosis, chromomycosis, generalized forms of dermatophytes, pityriasis and for oropharyngeal and vulvo-ginal candidiasis. The dose of fluconazole is 100 mg per day, orally or intravenously. The dose of itraconazole is 100-200 mg per day, orally.



Triazole ring

Fluconazole causes headache, vomiting and diarrhea in about 1-4% of patients. Mild, subclinical liver damage with elevation of transaminases can sometimes occur. Similar effects are caused by itraconazole, although its use is contraindicated in pregnancy (because it showed teratogenic effects in rats).

Fluconazole is excreted unchanged in the urine, and itraconazole is metabolized in the liver to inactive metabolites that are excreted in the urine or bile.

Voriconazole is a newer triazole with a very good effect on 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 CIP 3A4 isoform of cytochrome P 450, 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 appear (prolongation of the QT interval in E KG). In addition, voriconazole blurs vision and causes photophobia; therefore, patients taking it must not drive or operate machinery. Fever and liver damage are rare when voriconazole is used.

Posaconazole also inhibits ergosterol synthesis, and is active both in vitro and in vivo against Aspergillus, Candida, Coccidioides immitis, Fonsecaea pedrosoi (chromobla-stomycosis) 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 in the prophylaxis of fungal infections in patients with acute myelogenous leukemia or myelodysplastic syndrome receiving chemotherapy. The main adverse effects of posaconazole are gastrointestinal complaints, an increase in body temperature and an increase in bilirubin.

Allilamines

The most important representative of allylamine is **terbinafine**. This medicine can be applied orally or topically on the skin. Terbinafine inhibits the squalene-epoxidase enzyme, thereby preventing the synthesis of ergosterol in the fungal membrane. First of all, it is effective in the treatment of epidermophytes (which cause fungal infections of the skin and nails), while it has a weak 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 in this way take in griseofulvin in large quantities. Griseofulvin binds to the microtubules of fungal cells, interferes with their numerous functions (transport through the cytoplasm, dividing 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 has to be used for several months for the treatment of fungal infections of hairy parts and nails, it is necessary to periodically control the patient's blood count and liver cell damage parameters (transaminases). The drug is teratogenic, so its use during pregnancy is contraindicated. The patient should be warned not to drink alcohol during griseofulvin therapy, because griseofulvin has an effect similar to disulfiram.

Medicines for local therapy of dermatophytes

Often, a fungal infection affects only a limited area of the skin. Then it is enough to apply some antifungal preparation locally, in the form of creams, lotions or ointments. Imidazoles (econazole, clotrimazole, miconazole), terbinafine, ciclopirox olamine, haloprogin, tolnaftate can be applied locally. The effectiveness of these preparations is very similar, and the side effects are minimal. All of them also work well on pityriasis, although for its treatment it is enough to apply only keratolytic (10% salicylic acid ointment).

Special issue represents locally treatment onychomycosis, due to weak penetration antifungal medicines through the nail board. All to recently is local therapy been ineffective, yes would be se past years appeared two medicine which have got excellent penetration

through the nail plate and after local applications achieve healing the code about 80% of patients. That are tavaborole and elfinaconazole. ***Tavaborole*** inhibits synthesis transport RNA in cells fungus and ***elfinaconazole*** prevents synthesis ergosterol, as well as the others azoles. Theirs wider use is limited with a high price for now.

MEDICINES AGAINST VIRUSES

Viruses are intracellular parasites, which use the building materials 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 they are virus-specific. It is precisely these enzymes that represent 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. According to whether they contain DNA or RNA, viruses are divided into DNA and RNA viruses. Pathogenic **RNA** viruses are: ***arbor viruses*** (causing yellow fever and tick-borne encephalitis), ***arenaviruses*** (causing meningitis and Lassa fever), ***hepacivirus*** (causing hepatitis C), ***orthomyxoviruses*** (causing influenza), ***paramyxoviruses*** (causing mumps and smallpox), ***picornaviruses*** (causing respiratory infections, meningitis, poliomyelitis), ***rhabdoviruses*** (causing rabies), ***rubella virus*** (causing rubella) and ***retroviruses*** (causing AIDS). Pathogenic **DNA** viruses are: ***adenoviruses*** (causing inflammation of the tonsils and respiratory infections), ***hepadnaviruses*** (causing hepatitis B), ***herpesviruses*** (causing herpes of the lips and genital organs, herpes-zoster, chicken pox and cytomegalovirus infections), ***papillomaviruses*** (causing condiloma) and ***poxviruses*** (the causative agent of smallpox).

Virus reproduction in the host cell proceeds through the following stages: (1) attachment to the cell and penetration into it; (2) removing the protein coat ("undressing" the nucleic acid); (3) synthesis of virus components; (4) assembly of the viral particle ("coating" the nucleic acid), and (5) release from the host cell. Synthesis of their DNA components is carried out by viruses in that their DNA serves as a matrix for transport RNA, which encodes the synthesis of viral proteins on the ribosomes of the host cell. RNA viruses do this in several ways: their RNA can be directly a matrix for transport RNA , or the RNA of the virus acts as a transport RNA , or on the basis of the viral RNA , DNA is created (using the reverse transcriptase enzyme), which then serves as a matrix for synthesis. transport RNA .

MEDICINES _ For infections herpes viruses

Infections with Herpes simplex virus (type 1 - causative agent of herpes labialis, type 2 - 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, which are phosphorylated to triphosphate in the host cell, and then inhibit the viral DNA polymerase. The viral enzyme thymidine kinase (which is required for the phosphorylation of acyclovir) has a much higher affinity for acyclovir triphosphate than human cell thymidine kinase; therefore, acyclovir accumulates in cells affected by the virus.

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 mentioned indications, and has considerable toxicity: liver damage, confusion, thrombocytopenia and/or anemia. That is why today vidarabine is mainly used topically, in the form of eye ointment, to treat 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 infections with the herpes virus, for severe, recurrent infections with genital herpes, but also for infections with the herpes zoster virus (only in severe cases of chicken pox or herpes zoster). After oral administration, acyclovir is incompletely absorbed. About 20% of the drug in the 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 (glomerular filtration and tubular secretion), mostly unchanged. It stays in the body for a relatively short time: the half-elimination time is only 3-4 hours.

Acyclovir is generally well tolerated, and in most patients it 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 previously had kidney disease. To avoid this, the patient should be well hydrated. In immunocompromised patients, acyclovir can cause the appearance of thrombocytic 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, valaciclovir was synthesized, a pro-drug that is well absorbed and then converted into acyclovir in the liver and intestinal wall. In this way, the serum concentrations of acyclovir are achieved 3 to 5 times higher than the concentrations obtained by the administration of acyclovir alone. Valacyclovir has the same side effects as acyclovir; its main advantage is in less frequent dosing (500 mg is given every 12 hours, orally). Valacyclovir is used to treat recurrent genital herpes and moderate-to-severe forms of herpes zoster.

Herpes simplex eye infection can also be treated with local application ***of idoxyuridine***, which is too toxic for systemic use. Idoxyuridine also inhibits DNA polymerase. ***Trifluridine*** is another drug that is also used topically to treat keratoconjunctivitis caused by herpes viruses type 1 and 2. It is a fluorinated pyrimidine nucleoside, which after phosphorylation inhibits the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate and then competes with deoxythymidine triphosphate for incorporation in the DNA of the virus and the host cell. Both drugs can cause clouding of the cornea after long-term use.

In the last ten years, a large number of drugs that inhibit the DNA polymerase of the virus have been approved for use. Some of them (famciclovir, penciclovir), in order to become active in the infected cell, require the presence of *viral* thymidinekinase, and some do not (foscarnet, cidofovir).

Penciclovir is an acyclic analogue of guanosine, which acts by the same mechanism as acyclovir on the synthesis of herpes virus DNA. ***Famciclovir*** is a prodrug (diacetyl ester of penciclovir), which after absorption is converted in the liver to penciclovir. Penciclovir is only used topically to treat herpes on the lips. Famciclovir is used systemically, which is well absorbed after oral administration, and ensures the bioavailability of penciclovir of 77%. Like aciclovir, penciclovir is slightly bound to plasma proteins (20%) and penetrates well into all tissues. It is eliminated through 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: 500 mg / 8 hours, orally). Famciclovir can cause confusion and hallucinations, and rarely bone marrow suppression. In experiments on animals, the carcinogenic effect of famciclovir was shown, as well as the inhibitory effect on spermatogenesis.

Since viral thymidine kinase is required for acyclovir, valacyclovir and famciclovir, if resistance to one of them appears due to a mutation in the gene encoding that enzyme, then the virus becomes resistant to the other two drugs as well (cross-resistance**)**. There is no cross-resistance with foscarnet and cidofovir.

Cidofovir is an acyclic analogue of cytosine, which after intracellular conversion to cidofovir diphosphate inhibits the activity of viral DNA polymerase. Since its conversion occurs under the action of host cell enzymes and not viral enzymes, the active form of the drug is found in the same concentrations in both infected and non-infected cells.

Cidofovir is poorly absorbed, so it can only be administered intravenously. It is quickly excreted unchanged in the urine (half-elimination time 2.5 hours), but it remains much longer (several days) inside the cells, bound to phosphocholine. It is used for the treatment of herpes simplex infections that are resistant to acyclovir, for the prevention and treatment of cytomegalovirus retinitis in people with AIDS (5 mg / kg intravenously, once weekly), for the treatment of condyloma (Condylomata accuminata) and Molluscum contagiosum, and for the treatment of polyomavirus-associated multifocal leukoencephalopathy.

Cidofovir is **a nephrotoxic** drug, because during tubular secretion it damages tubule cells, leading to proteinuria, glycosuria, increased creatinine, and sometimes Fanconi syndrome. Cidofovir also causes

anterior uveitis and neutropenia relatively frequently; decreased intraocular pressure and metabolic acidosis may occur rarely. Cidofovir has shown carcinogenic, embryotoxic and teratogenic effects in animal experiments.

Fanconi syndrome means a generalized disorder of the functioning of the proximal tubule of the nephron, which is manifested by hypophosphatemia, a reduced level of uric acid in the serum, proximal tubular acidosis, and the appearance of protein and glucose in the urine.

Note: aciclovir, penciclovir and cidofovir are secreted in the renal tubules by the same transport system as probenecid; this drug can 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 in a small percentage, and penetrates very well into many tissues and body fluids (eg, the vitreous body of the eye). It especially accumulates in the bones, as a result of which it is slowly eliminated from the body (remains for several days), as an unchanged drug in the urine.

Foscarnet is used to treat cytomegalovirus retinitis in patients with AIDS, and to treat acyclovir-resistant herpes virus or varicella-zoster virus infections in immunocompromised individuals.

Foscarnet is **a nephrotoxic** drug, which therefore leads to disturbances in the homeostasis of minerals in the serum: hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia. Reduced concentrations of potassium, calcium and magnesium can cause tetany, paresthesias, arrhythmias or convulsions. Nephrotoxic effect can be best prevented by good hydration of the patient. Due to the high concentration it reaches in the urine, foscarnet can cause **ulcerations** on the external genital organs.

Docosanol is another drug used to treat herpes simplex virus infection. It is a long-chain, saturated alcohol that prevents virus entry into cells by inhibiting the fusion of the virus envelope with the host cell membrane. It is used exclusively topically, for cold sores. There are no side effects, so it is issued without a prescription. Docosanol is only effective if administered in the prodromal phase, before the vesicles have yet erupted.

Cytomegalovirus infections are especially severe in newborns who get them from their mothers during intrauterine life. Most organs are damaged, especially the central nervous system. Cytomegalovirus infections respond well to ***ganciclovir***, another acyclic analogue of guanosine that after phosphorylation inhibits DNA polymerase of the virus. Once inside the cell, ganciclovir requires phosphorylation by the viral protein kinase pUL 97 in order to become active. 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. Orally, ***valganciclovir*** is more often used, a pro-drug that is well absorbed, and then quickly turns into ganciclovir in the liver, reducing the bioavailability of ganciclovir by about 60%. 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 to treat cytomegalovirus retinitis in immunocompromised individuals, and to prevent cytomegalovirus infection in organ transplant patients. The most pronounced side effect of this drug is **bone marrow suppression**; neutropenia and anemia occur in 30% of patients, and thrombocytopenia in 10%. Teratogenic and carcinogenic effects of ganciclovir have also been shown in experiments on animals. Zidovudine, an AIDS drug, potentiates the myelosuppressive effect 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.

Fomivirsen ***(***the so-called "antisense" oligonucleotide) is used locally for the treatment of cytomegalovirus retinitis. Fomivirsen is complementary to the I E2 region of cytomegalovirus transport RNA (tRNA). When bound to tRNA, fomivirsen prevents the synthesis of virus proteins, and thus their reproduction. The drug is injected directly into the vitreous body of the eye, and is used to treat cytomegalovirus retinitis in AIDS patients who have not responded to other therapy. In about 25% of patients, fomivirsen can cause iritis.

The others antivirus medicines

Infections with most RNA viruses, respiratory syncytial virus infection, hepatitis C virus infection (but only in combination with interferon alfa), viral hemorrhagic fever and Lassa fever can be treated with ***ribavirin*** . Ribavirin is a guanosine analogue, which interferes with the synthesis of viral RNA. It also causes mutations in the RNA virus, so that virions are formed that are unable to reproduce further.

Ribavirin is used in the form of an aerosol, and orally. It is well absorbed, so the bioavailability is 64%, and it can be increased if the drug is taken together with a fatty meal. Ribavirin is metabolized in the liver to a triazole carboxyl metabolite, which, together with the unchanged drug, is eliminated through the urine. 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 via aerosol**, lung and heart function** may deteriorate, while **hemolytic anemia** often occurs after oral administration. When administered together with interferon alfa, ribavirin potentiates its side effects: fatigue, insomnia, depression, pancreatitis. Ribavirin is **mutagenic, teratogenic and embryotoxic**. It is contraindicated in persons with sickle cell anemia and with hemoglobinopathies.

Smallpox (Variola vera) can be alleviated by the use ***of methasone*** at the beginning of the disease. Metisazone prevents the assembly of viruses *after* the synthesis of viral DNA, and thus their reproduction. The dose is 3 g /day, orally.

Antibodies can also be used in the therapy of viral infections: ***gammaglobulin*** and ***hyperimmune gammaglobulin***. Gamma-globulin is a preparation of globulin obtained from the serum of blood donors, and hyperimmune gammaglobulin is obtained from the serum of only people who have suffered from *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 mostly the IgG type, while the 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 applied at the beginning of the disease.

Globulins are administered intramuscularly or intravenously. After application, their protective effect lasts 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 a possibility of an allergic reaction, which is more common in people who previously had hypo- or aga-maglobulinemia, with repeated administration and with intravenous administration. Intravenous administration of gammaglobulin should be slow, because otherwise reddening of the face, 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 transmission of pathogenic micro-organisms and infection (eg hepatitis B, C or AIDS virus). High doses of gammaglobulin can cause aseptic meningitis in some patients. Finally, gammaglobulins interfere with the formation 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 a viral infection. There are three types of interferon: ***interferon alpha*** (type 1, mostly produced in leukocytes), ***interferon beta*** (type 1, mostly produced in fibroblasts) and ***interferon gamma*** (type 2, produced by killer cells and T lymphocytes) . Interferons do not act directly on viruses, but instead trigger a series of mechanisms that interfere with virus reproduction. They bind to membrane receptors and trigger at least two signaling mechanisms: the activation of cellular ribonucleases that degrade the single-stranded RNA of the virus and the 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 longer, up to 72 hours. Interferons are removed from the blood by degradation in the liver and kidneys.

Interferons alfa 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 condyloma. In the treatment of hepatitis C, interferon alfa is combined with ribavirin. Interferon beta is used in the treatment of multiple sclerosis, while interferon gamma is used to relieve 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 to it often develops after repeated doses. There are significant side effects on the central nervous system: depression with *suicidal tendencies*, weakening of memory and concentration, insomnia and anxiety. Bone marrow suppression, gastrointestinal complaints (vomiting, diarrhea, anorexia), hair loss, and reduced 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 analog that, after phosphorylation in the cell, inhibits the DNA polymerase of the hepatitis B virus and the reverse transcriptase of the AIDS virus. That is why 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 quickly 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 serum levels of alanine aminotransferase (ALT) , creatine kinase, and lipase. It can cause pancreatitis in children.

Remdesivir is a pro-drug from which an adenosine analog is produced in the body, which inhibits the RNA polymerase of the SARS-CoV-2 corona virus. This medicine is effective in the treatment of severe forms of COVID-19 (coronavirus infection 19), because it shortens the time to recovery, and in certain subgroups of patients (e.g. those who require oxygen therapy) it also reduces mortality. Remdesivir is administered intravenously, 100 mg once a day for 5 days; it is generally well tolerated, the most common side effects being an increase in serum transaminases and nausea.

Palivizumab is a humanized monoclonal antibody against the F -protein on the surface of the respiratory syncytial virus (RSV). Contains 95% human and 5% murine amino acid sequences. It neutralizes the virus and prevents it from binding to host cells. It is used only for the prophylaxis of infection with RSV, during the winter season, in the form of intramuscular injections once a month. It is used only in high-risk children: children under 2 years old 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 as follows: (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 fuse with human plasmacytoma cells, so that the hybrid cell now makes large amounts of antibodies; (4) only those hybrid cells that create antibodies against the desired antigen are isolated; (5) the isolated hybrid cells are multiplied (cloned), and the antibodies they produce are isolated.

Treatment syndrome acquired immunodeficiency (AIDS , A IDS)

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, so that it becomes more susceptible to the development of infections and malignant diseases. The HIV virus is an RNA virus, with only one strand of RNA . It enters *CD 4+ T lymphocytes and macrophages*, where it multiplies, reducing the number of these cells and creating immunodeficiency. It usually takes 3-10 years from the moment of infection until the immunodeficiency syndrome is fully manifested. The virus reproduces by creating DNA on the basis of its RNA , with the help of ***reverse transcriptase enzymes*** , which goes into the nucleus of the host cell, is incorporated 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 manifest disease. That is why therapy is started as early as possible. It used to be thought that therapy should be started when the number of CD 4 lymphocytes is less than 350/ μl, and the number of viral particles is more 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. inhibitors of virus entry into lymphocytes, and
6. viral integrase inhibitors.

Most often, a combination of 2 nucleoside inhibitors with one non-nucleoside inhibitor or one protease inhibitor is used; such a combination is called "highly active antiretroviral therapy".

Nucleoside inhibitors of reverse transcriptase are phosphorylated in cells to the triphosphate form, and then under the action of reverse transcriptase they are incorporated into the DNA of the virus. However, since they lack the 3'-hydroxyl group, they lead to the termination of the growth of the viral DNA chain, preventing further reproduction of the virus. Since they also inhibit DNA polymerase in mitochondria, they can cause lactic acidosis, steatosis of the liver and its enlargement. Therefore, laboratory signs of hepatotoxicity must be monitored when using all drugs from this group. The first drug from this group was ***zidovudine*** (azidotymidine), an analog of thymine. 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 through the urine. In addition to the treatment of AIDS, 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 significantly less frequently.

Stavudine is a nucleoside analogue of thymidine, which, in addition to the treatment of AIDS, is also used for the prophylaxis of infection after exposure to infectious material. It is well absorbed, is not metabolized, and is mostly excreted through 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 the phosphorylation of stavudine, and thus its activity).

Didanosine is an analogue of adenosine, which, in addition to the treatment of AIDS, is also used for the prophylaxis of infection after exposure to infectious material. Bioavailability after oral administration of this drug is about 40%; the drug is metabolized in the liver, like other purine bases. Side effects 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, as 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, whose specific side effect is hyperpigmentation of the palms and soles. ***Abacavir*** is a guanosine analogue, which, in addition to the treatment of AIDS, is also used for the prophylaxis of infection after exposure to infectious material. It is often prepared in fixed combinations with zidovudine or lamivudine. Abacavir is intensively metabolized in the liver, under the action of alcohol dehydrogenase. About 5% of patients who receive this medicine develop a potentially *fatal allergic reaction*, manifested by fever, measles and respiratory symptoms.

Zalcitabine is the least effective of all nucleoside reverse transcriptase inhibitors. It is an analogue of cytidine, which is used to treat AIDS. It is well absorbed after oral administration, is not metabolized, and is excreted unchanged via 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 pro-drug, which is transformed in the body into ***tenofovir***, a nucleoside analogue of adenosine.

Tenofovir is effective in the treatment of AIDS even when resistance to nucleoside reverse transcriptase inhibitors develops. It has low bioavailability after oral administration (25%), is not metabolized, and is excreted unchanged via the kidneys. Tenofovir is *well tolerated*, as it does not have a toxic effect on mitochondria like nucleo-wall 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 quickly develops, so they are *never used alone*, but only together with nucleoside reverse transcriptase inhibitors. Since they are metabolized in the liver, and thereby induce cytochrome P 450 enzymes, these drugs enter into numerous interactions with other drugs that use the same metabolic pathway. The absorption of non-nucleoside reverse transcriptase inhibitors and protease inhibitors is greatly influenced by the acidity of the gastric juice and the time of taking the drug in relation to taking a meal. Therefore, attention should be paid to simultaneous intake of proton pump blockers or N_2 blockers.

In addition to the treatment of AIDS, ***efavirenz is*** also used for the prophylaxis of infection after exposure to infectious material. The drug may cause measles and an increase in liver enzymes and serum cholesterol. It has a strong effect on the central nervous system, causing: insomnia, euphoria, agitation, thought disorder, nightmares and *hallucinations*. It has *a teratogenic* effect, so patients should use contraception. Efavirenz induces CIP 3A4, and inhibits CIP 2 C 9 and CIP 2 C 19, so it enters into numerous interactions with other drugs that are metabolized by the same enzymes.

Nevirapine is only used to treat 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 CIP 3A4. ***Delavirdine*** is also only used to treat AIDS. The most common side effect is measles with itching, which passes over time. ***Etravirine*** similar to efavirenz, it induces CIP 3A4, and inhibits CIP 2 C 9 and CIP 2 C 19. Sometimes etravirine causes a severe allergic reaction with measles, which can end with the failure of certain 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 from this group.

Viral protease inhibitors are used in AIDS therapy, 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 a central accumulation of adipose tissue, similar to that of corticosteroid administration (buffalo hump, breast enlargement). Hepatotoxicity is also possible. Since they are metabolized in the liver under the influence of CIP 3A4, 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 all of them, and interacts the most with other drugs, because in addition to inhibiting CIP 3A4 and CIP 2 D 6, it induces CIP 1A2. Today, it is used exclusively together with other protease inhibitors, in order to increase their concentration in the serum due to cytochrome inhibition. ***Indinavir,*** in addition to side effects characteristic of the entire group, causes nephrolithiasis, especially in children (up to 30%); in order to prevent this unwanted effect, it is necessary for children to consume 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 in the form of a solution for oral administration, which contains a lot of *propylene glycol*; therefore, it must 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 pro-drug, which is converted to amprenavir. This group of drugs also includes ***saquinavir, lopinavir, darunavir and atazanavir***. This last drug has specific side effects: it prolongs the QT interval and interferes with the excretion of bilirubin. ***Tipranavir*** is a newer protease inhibitor that is given for resistance to other drugs from this group. May cause hepatitis as a side effect.

Inhibitors of viral entry into lymphocytes

Enfuvirtide prevents the entry of the HIV virus into lymphocytes by blocking the viral transmembrane protein **gp 41**, which enables the fusion of the virus membrane with the lymphocyte membrane, while ***maraviroc*** does so by blocking the chemokine **CCR 5** receptors on lymphocytes for virus glycoproteins.

While enfuvirtide as a drug of protein nature is administered parenterally, maraviroc is administered orally. Both drugs are used only as additional therapy with reverse transcriptase inhibitors, in patients who have not responded well to primary therapy.

Viral integrase inhibitors

Raltegravir , elvitegravir, and dolutegravir are inhibitors of viral integrase, the enzyme that incorporates viral DNA into the host's chromosomes, thereby enabling viral replication. Raltegravir, elvitegravir and dolutegravir are administered orally. They are used in combination with other antiretroviral drugs to treat patients in 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 works against some strains of the virus that are resistant to raltegravir and elvitegravir.

AIDS drugs and pregnancy

To prevent the transmission of the HIV virus from mother to child, a pregnant woman should continue combined antiretroviral therapy throughout pregnancy. Antiretroviral drugs that penetrate the placenta well and have less potential side effects on the mother and the fetus are: zidovudine, lamivudine, nevirapine, atazanavir, lopinavir and ritonavir. Therapeutic regimens administered during pregnancy should be based on the previously listed drugs whenever possible. Mothers with AIDS who have an HIV -negative newborn should not breastfeed, because the risk of transmission of the virus through breastfeeding is 10-20%.

DRUGS AGAINST THE FLU VIRUS

Medicines that act on influenza viruses are applied only to patients who are at special risk (chronic respiratory disease, significant cardiovascular disease, chronic kidney disease, immunosuppression, diabetes and age over 65).

Once widely used, amantadine is increasingly avoided. Today, zanamivir or oseltamivir are used in adults, and only oseltamivir in children. The condition is that the therapy starts within 48 hours of the onset of symptoms .

are three types of influenza viruses: A, B and C. Only types A and B cause significant disease in humans. For the prevention of influenza, it is best to use the vaccine, which is given to persons at special risk (see above).

Amantadine is a synthetic tricyclic amine, and ***rimantadine*** is its alpha-methyl derivative. Both drugs inhibit the M_2 ion channel in the membrane of influenza virus type A ; they have a weak effect on type B. M_2 is a channel for hydrogen ions, which, when blocked, prevents the "undressing" of the viral RNA. If these drugs are administered within 48 hours of the onset of symptoms, the duration of elevated temperature and discomfort is shortened by 1-2 days, and virus excretion is shortened. 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 quickly 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 through 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: urine retention and dry mouth. Both amantadine and rimantadine can cause convulsions. Amantadine is teratogenic, and rimantadine is embryotoxic.

Zanamivir is a viral neuraminidase inhibitor. 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. About 15% of the ingested dose is absorbed into the blood and then excreted unchanged through the kidneys. Zanamivir is used for treatment (shortens the duration of the disease by 1 day) and prophylaxis of infection with influenza A and B , 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 as an inhalation; for now it is only used in Japan.

Oseltamivir is also a neuraminidase inhibitor of the influenza virus. It is administered orally, it is well absorbed, and then it is converted into the active form of oseltamivir carboxylate in the liver. The unchanged drug and the active metabolite are excreted by the kidneys. Works well on influenza A and B; in treatment it is used in children older than one year and adults, and in prevention it is used only in people older than 13 years. Reduces the duration of symptoms by half a day, and shortens absence from work by two whole days; it also reduces the incidence of complications. It can prevent influenza virus infection in 90% of exposed people.

Oseltamivir is well tolerated: nausea and vomiting occur in 3-7% of patients, and bronchitis, dyspnea and liver cell damage occur rarely.

Peramivir is another new neuraminidase inhibitor, which is administered intravenously as a single dose. It is not significantly different from oseltamivir in terms of effectiveness, but it 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, which do not tend to become chronic. After the acute phase, the patient is definitively cured. Hepatitis B and C represent the biggest problem, because after an acute infection they go into a chronic phase; 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 alfa, entecavir and tenofovir disoproxil fumarate. **Pegylated interferon α**is a conjugate of interferon αand monomethoxy polyethylene glycol. Such "pegylated" interferon αis actually a depot preparation, which can be applied once a week, subcutaneously (otherwise, ordinary interferon was applied three times a week), and enables higher and more stable concentrations of interferon alpha to be achieved in the blood. **Ente-kavir** is a guanosine analog 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 DNA polymerase of the hepatitis B virus . ***Telbivudine*** is an analog of thymidine, which after phosphorylation is incorporated into the DNA of the hepatitis B virus . It has a hepatotoxic effect and damages the striated muscles. These drugs are applied as monotherapy at the beginning of treatment, and later they can be combined with each other, if the patient did not respond to monotherapy in an appropriate way. Treatment of the chronic form of hepatitis B lasts at least one year.

Lamivudine and adefovir as second-line drugs (an acyclic analog of adenosine monophosphate, which inhibits viral DNA polymerase) can be used in the treatment of hepatitis B. Adverse effects of adefovir are: damage to kidney function, asthenia and worsening of hepatitis after discontinuation of the drug. Lamivudine and adefovir are used less and less today, because their effectiveness is significantly lower than first-line drugs, and because virus resistance to them develops more often and faster.

Hepatitis C requires treatment if patients are positive for hepatitis C viral RNA . Only a few years ago, pegylated interferon alfa and ribavirin were the backbone of chronic hepatitis S therapy . Oral therapy for chronic hepatitis S is now available, which is very effective and can completely cure almost all patients in just 12 weeks.

A national program is active in Australia to use these new drugs to eradicate the hepatitis S virus in the human population; general practitioners are authorized to prescribe these drugs without consulting specialists .

The key moment in the treatment of hepatitis S is to determine the genotype of the virus and the concentration of viral particles, because the choice of medicine and the prognosis depend on it . Combinations of drugs are always used, and they are fixed . The following drug combinations are present in practice:

1. **Sofosbuvir + velpatasvir** is a combination that is applied for 12 weeks , and works on all 6 genotypes of the hepatitis S virus . Sofosbuvir inhibits NS5B RNA polymerase, and velpatasvir NS5A, i.e. non-structural protein 5A, which plays an important role in the assembly of the viral particle and its exit from the cell . Fosbuvir interacts with amiodarone, causing symptomatic bradycardia , as well as with other drugs that induce cytochromes .
2. The combination **with ofosbuvir + daclatasvir** is not fixed, it is used for 12 weeks . In this combination with ofosbuvir, it works only on genotypes 1a and 1b , and daclatasvir on all genotypes . D akalatasvir inhibits NS5A, i.e. non-structural protein 5A is essential for the assembly of the viral particle and its exit from the cell . If the patient receives statins at the same time, their doses must be reduced due to daclatasvir .
3. **Sofosbuvir + ledipasvir** , a fixed combination, is used for 8-12 weeks , and acts on 1, 4 and 6 genotypes of the hepatitis S virus (sofosbuvir acts only on genotypes 1a and 1b , and ledipasvir on 1, 4 and 6) . Sofosbuvir inhibits NS5B RNA polymerase, and ledipasvir 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** works only on genotype 1, and is used for 12 weeks . Paritaprevir – inhibits NS3/4A protease important in post-translational protein modification ; ritonavir – increases the concentration of paritaprevir by inhibiting its metabolism on cytochromes ; o mbitasvir – inhibits NS5A ; and d asabuvir – 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 applied for 12 weeks . Elbasvir inhibits NS5A, ie. non-structural protein 5A, which plays an important role in the assembly of the viral particle and its exit from the cell , a g razoprevir inhibits NS3/4A protease important in post-translational modification of proteins . And these drugs interact with inducers of cytochromes.

ANTIMALARIAL MEDICINES

Malaria is caused by intracellular protozoa from the Plasmodium group . The mosquito feeds on the blood of a person suffering from malaria, and on that occasion it takes in Plasmodium gametocytes (male and female). Gametocytes fuse in the stomach of the mosquito and a zygote is formed. The zygote penetrates the stomach wall and transforms into an oocyst, which upon maturation releases a large number of sporozoites. Sporozoites enter the mosquito's bloodstream and salivary glands. When a mosquito bites a healthy person, the sporozoites are injected into the blood. Through the blood, they reach the liver cells, where they enter and reproduce many times over (this is the so-called exoerythrotic phase of development). Spraying the infected liver cells ends the exoerythrocytic phase and the released merozoites now enter the erythrocytes. Plasmodium species falciparum and Plasmodium malariae completely leave the liver, while Plasmodium ovale and Pla - smodium vivax remain partly in the liver cells in the form of hypnozoites, which can later be reactivated and lead to relapse of the disease. Merozoites grow in erythrocytes (feeding on hemoglobin) and multiply to form conglomerates called schizonts. When they grow enough, they cause erythrocytes to burst and release a large number of new merozoites into the blood, which enter new erythrocytes. In addition to merozoites, schizonts also give rise to gametocytes that can infect ″healthy ″mosquitoes, thereby closing the cycle.

Since the splashing of erythrocytes and the release of merozoites occur synchronously (at once), the clinical picture of malaria occurs in attacks. In Plasmodium falciparum attacks occur every 48 hours, with Plasmodium vivax and Plasmodium ovale every 72 hours, and Plasmodium malariae every 96 hours.

Antimalarial drugs act on schizonts in erythrocytes by interfering with the utilization of hemoglobin. The drug of choice is still **chloroquine** , except in regions dominated by chloroquine-resistant falciparum malaria. Plasmodium feeds on hemoglobin, whereby chem appears 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. In resistant forms, other quinolines are used: **quinine** (a natural alkaloid from the bark of the quinine tree) and **mefloquine** . All amino-quinolines act only on erythrocytic forms of malaria - schizonts. Adverse effects are similar: they act on excitable tissues, the CNS (ringing in the ears, visual disturbances, confusion, "quinine drunkenness", headache) and the heart (prolongation of the Q RS 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 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. They then do not actually prevent malaria infestation, but prevent malaria attacks after infestation occurs.

Medicines that interfere with the synthesis of folic acid in the parasite can be used for resistant forms of malaria. 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 during pregnancy, as well as for the prevention of malaria. **Atovaquone/proguanil** combination is used to treat Pl. falciparum that is resistant to chloroquine. It can also be used in prevention. Atovaquone inhibits electron transport, synthesis of AT R 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. That is why it is used together with drugs that interrupt the attack of malaria for the eradication of malaria in patients infected with Plasmodium ovale and Plasmodium vivax . Primaquine is transformed in the liver to an active metabolite. Its side effects are similar to side effects of 4-aminoquinoline: headache, itching, gastrointestinal disorders and hemolytic anemia in people with glucose-6-phosphate dehydrogenase deficiency. Primaquine is applied for a total of 14 days; a new drug that acts on hepatic forms of parasites and on gametocytes - **tafenoquine** - has been in use since recently . The effectiveness and safety of tafenoquine is almost the same as that of primaquine, but it has one important advantage - it is administered only in one dose.

QING - HAO plant and known as qinghaosu has been put into practice . It contains lactone ***artemisinin*** with endoperoxide, which is effective against erythrocytic forms of malaria. Heme and divalent iron ingested by the parasite catalyze the opening of the peroxide bridge in the artemisinin molecule; the consequence of that reaction is the creation of free radicals, which lead to the death of the parasite. So far, no resistance of malaria parasites to the mentioned drug has been observed.

Artemisinin can only be administered orally, as it is insoluble. Absorption of artemisinin is incomplete (bioavailability 43%). Artemisinin derivatives have been synthesized that can be administered intramuscularly: artemether, artesunate and arteether. Both artemisinin and its derivatives are metabolized in the liver, via cytochrome CIP 3A4. Most of these preparations have a short half-elimination time (a few hours), except for arteether (the half-elimination time 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. That is why artemisinin and its derivatives are not used in prophylaxis, but only in the treatment of malaria.

More one medicine se uses alternatively in treatment malaria : ***halofantrine*** . It acts only on the erythrocyte 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-elimination time of halofantrine is two days, and the half-elimination time of its metabolite is 3-5 days.

Halofantrine causes itching and hives on the skin. In the heart, it prolongs the QT interval, so it 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

Amoebae are protozoa (Entamoeba histolytica) that parasitize in the small and large intestine of humans. They exist in a cystic, non-invasive form that is located in the lumen of the intestine and in a vegetative form (trophozoites) that penetrates the wall of the intestine and further, through the blood to the liver.

Metronidazole (nitro-imidazole) works best on vegetative forms of amoeba, which acts cytotoxic 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 works well on giardiasis, trichomoniasis, blastocyst infestation, Balantidium coli , to anaerobic bacteria and to a parasite from the group of worms, Dracunculus medinensis - a .

Metronidazole can be administered both orally and parenterally, for at least 15 days. It penetrates perfectly into all tissues (and the CNS). Less than 20% of the drug is bound to plasma proteins. It is metabolized in the liver, and the unchanged drug and metabolites are excreted in the urine. Metronidazole works well on amoebas in the intestinal wall and on amoebas in the liver abscess, but it does not work at all on cystic forms in the lumen of the intestine! Therefore, it must be applied together with a luminal amoebicide.

Metronidazole causes a metallic taste in the mouth, headache, turns the urine dark and can cause peripheral neuropathy after long-term use. It also interferes with the metabolism of alcohol (blocks aldehyde dehydrogenase), so alcohol consumption during metronidazole therapy is accompanied by the accumulation of acetaldehyde (redness of the face, nausea, vomiting).

Another nitro-imidazole that can be used in the treatment of invasive forms of amoebiasis is ***tinidazole*** . Tinidazole interferes with the parasite's DNA synthesis and breaks the DNA chains . In addition to amoebas, it works well on Giardia lamblia and Trichomonas vaginalis , on 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 has a good effect on cystic forms of amoeba in the intestinal lumen . In the intestinal lumen, this drug is chemically broken down into furoate and diloxanide, which destroys 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.

In the past iodoquinol and clioquinol were used to treat amoebiasis, but they were shown to have marked toxicity: iodoquinol enlarged the thyroid gland, and clioquinol caused subacute myelooptic neuropathy followed by vision loss.

Sometimes amoebic liver abscesses do not respond to metronidazole. Medicines are then given that concentrate in the abscess and have an amebicidal effect. These are the antimalarial **chloroquine** and the ipecacuan alkaloid **emetine in the form of dehydroemetine**. Emetine should be administered only in hospital conditions due to its marked cardiotoxicity.

Some antibiotics also have an amebicidal effect. **Tetra-cyclines** lead to a decrease in the number of bacteria in the lumen of the intestine, which amoebas normally feed on. The aminoglycoside **paromomycin** has a direct amoebicidal effect, provided that it is administered orally. Antibiotics are used in the treatment of amoebiasis only if other amoebicides cannot be used (for example due to allergy).

TRICHOMONIASIS

Trichomoniasis is a very common genital infection caused by the protozoan Trichomonas vaginalis . It responds well to a seven-day administration of metronidazole (250 mg /8 hours, orally) or to just one dose of tinidazole of 2 grams. Both sexual partners should always be treated at the same time, regardless of the fact that one of them may not have symptoms!

LAMBLIASIS

Giardia lamblia is a protozoan that inhabits the duodenum and causes dyspeptic complaints. She is sensitive to metronidazole, which should be administered for 7 days (250 mg /8 hours, orally), and to tinidazole, which is administered in only one 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 lam - blia. It is used in children, in the form of an oral preparation, which is applied for 3 days. C. _ parvum and G. lamblia are found in the water of wells 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 works on C . parvum , fortunately with great efficiency.

The side effects of this drug are mild and transient, mainly on the digestive tract: vomiting, abdominal pain and diarrhea.

LEISHMANIASIS AND TRYPANOSOMIASIS

Leishmaniasis is an infection with protozoa from the genus Leish-mania. The reservoir of infection is 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 skin form is reflected in the formation of ulcers, and the visceral form (called "kala-azar") in the enlargement of the liver and spleen with an inflammatory syndrome.

Trypanosomiasis is caused by the protozoan Trypanosoma. In Africa, this disease is transmitted by "tice" flies, and in South America by cockroaches. 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 deterioration (the so-called " **sleeping sickness** "). The South American form of the disease is characterized by lymphadenopathy and a long-term febrile condition (Chagas disease).

For the treatment of leishmaniasis, organic compounds of pentavalent antimony are used: ***sodium stibogluconate*** and ***meglumin antimonate*** . They bind to sulfhydryl groups of parasite macromolecules, interfering with their function. Due to their irritating effect on the gastric and intestinal mucosa, antimony compounds are administered only parenterally. They are not metabolized in the body, but are excreted unchanged in the urine (half-elimination time is about 24 hours).

Sodium stibogluconate and meglumine antimonate are used to treat both visceral and cutaneous leishmaniasis. For the treatment of the visceral form of the disease, the antifungal preparation **amphotericin B** (liposomal preparation), which is less toxic than antimony compounds, is used as the drug of first choice . Instead of amphotericin B, **pentamidine** can be administered intramuscularly . Pentamidine interferes with the functioning of DNA , RNA and protein synthesis of parasites. The toxicity of pentamidine is reflected in the damage of kidney tubules, liver cells and cytopenia in peripheral blood.

A new drug for visceral leishmaniasis that is effective, cheap and with few side effects is ***miltefosine*** . Milte-fosine is a phosphocholine analogue that interferes with the functioning of the parasite's membrane and the transmission of signals across it. Healing with oral administration of miltefosine for 4-6 weeks is achieved in 97% of patients. Adverse effects consist of gastrointestinal complaints and a transient increase in serum creatinine.

Adverse effects of antimony compounds include pruritic measles, pancreatitis, liver damage, and an anaphylactoid reaction.

For the treatment **of trypanosomiasis** , pentamidine and suramin are used in *the first* line, followed by arsenic compounds, eflornithine, nifurtimox and benznidazole.

Pentamidine is used to treat infection with Trupanosoma brucei gambiense, and suramin is used to treat infection with Trupanosoma brucei rhodesiense.

Suramin leads to the death of trypanosomes, by a still incompletely known mechanism. It cannot be absorbed from the gastrointestinal tract, so it is administered only intravenously. It binds to plasma proteins very tightly, and therefore remains in the blood for months. It does not penetrate into 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 does not work against South American trypanosomes. In advanced disease, it is always used in combination with arsenic compounds.

In sensitive individuals, intravenous administration of suramin is accompanied by nausea, hypotension and loss of consciousness. After prolonged use, it can cause peripheral neuropathy and albuminuria.

Eflornithine inhibits the enzyme ornithine decarboxylase, which hinders the synthesis of polyamines in parasites. Like sura-min, eflornithine is administered intravenously. It does not bind to plasma proteins, so it is quickly excreted in the urine as an unchanged drug (half-elimination time is only 3 hours). It penetrates well into the central nervous system. It is used to treat the African form of trypanosomiasis and only Trupanosoma brucei gambiense. The most common side effects are anemia and leukopenia.

Arsenic compounds used to treat trypanosomiasis are ***melarsoprol*** and ***triparsamide*** . Arsenic from these molecules binds to sulfhydryl groups of parasite enzymes, and inactivates 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 measles. Melarsoprol is less toxic than tripar-samide.

Nifurtimox is a substance that after its reduction leads to the creation of free radicals. Since trypanosomes do not have enough enzymes to defend against free radicals (no catalase), lipid peroxidation and parasite death occur. The drug is well absorbed after oral administration. Meta-heals quickly; its metabolites are excreted in the urine.

Nifurtimox is used primarily to treat South American trypanosomiasis, but it can also be used for African forms of the 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, administered orally for two months. It creates free radicals and electrophilic metabolites in the organism, which then bind to macromolecules of the parasite and block their functions. It causes skin rash, peripheral polyneuritis and leukopenia.

TREATMENT OF SCABIES

Scabies is caused by the Sarcoptes insect scabiei which parasitizes the skin causing excruciating itching. Scabies is treated by applying a 25% preparation of benzyl benzoate to the skin for 3 consecutive days. Benzyl benzoate is not toxic. It should be applied to the entire skin of the body, except for the neck and head (because the parasite does not settle in those parts). In addition to benzyl benzoate, 0.3% lindane, an organochlorine insecticide, can be used. After application, leave it on the skin for 10 hours, then wash it off. Its application is more dangerous, because if it is applied excessively, it can be absorbed through the skin and cause convulsions. In the absence of other medicines, a traditional medicine is used: 5% elemental sulfur ointment. This medicine, however, must be applied much longer than the new medicines: it must be applied to the skin for 8 consecutive days. Since it is completely non-toxic, it can be used by pregnant women and infants.

Don't forget: always treat all family members at the same time when scabies appears!

TREATMENT OF LEGS

Head lice (Pediculus capitis) and pubic rash (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 plant-based insecticides, pyrethrins and permethrin. Lindane is more toxic and less effective than herbal insecticides that cause only mild skin irritation. After applying the shampoo and rinsing, the hair should be carefully combed with a thick comb dipped in a 10% solution of acetic acid (to remove nits, i.e. lice eggs and larvae).

Body lice (Pediculus corporis) is treated by exposing the clothing to hot steam in an autoclave (or, in wartime, in a " **Serbian barrel** ") and dusting the clothing with the organochlorine insecticide DD T.

TREATMENT OF HELMINTHIASIS

Helminths can parasitize humans in the intestinal lumen or in tissues. In the lumen of the intestines, roundworms (nematodes) and tapeworms (cestodes) parasitize, and in the tissues, tapeworms (filaria) and flukes (trematodes).

In our country, the most common nematodes are small (Enterobius vermicularis) and large (Ascaris lumbricoides) white worm. Trichuris are much less common trichiura , Strongyloides stercoralis and Anky - lostoma duodenale . Enterobius and ascaris can be successfully treated ***with mebendazole***, a benzimidazole preparation that inhibits the synthesis of microtubules and thus hinders the uptake of glucose into the parasites (enterobius 100 mg in one dose, ascaris 100 mg every 12 hours for three days). Mebendazole is absorbed very little (only 10% of the dose taken), so side effects are rare (abdominal pain, diarrhea). Mebendazole can also be used to treat hookworm and trichiura infestations.

Thiabendazole and ***albendazole*** are in the same group of benzimidazoles . Their mechanism of action is the same as that of mebendazole; thiabendazole additionally inhibits the enzyme fumarate reductase, which is necessary for the creation of adenosine triphosphate (ATP) . Thia-bendazole 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 together 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 not only on enterobius and ascaris but also on trichiura, trichinella, strongyloides and hookworm, so it can be used to eliminate the mentioned nematodes. Today, thia-bendazole is the drug of choice only for strongyloides and trichinosis, as there are less toxic drugs for other infestations.

Albendazole has the widest spectrum of action. In addition to nematodes, which are also affected by thiabendazole, albendazole also acts on 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 types of flukes (Opisthorchis sinensis , Clonorchis sinensis , Opistor - chis viverrini) respond well to albendazole.

Trichinella (nematode, Trichinella spiralis , which lives for a short time in the intestinal lumen and its 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).

Adverse effects of thiabendazole include neurotoxic effects (headache, drowsiness, confusion, hallucinations, tinnitus, paresthesias, visual disturbances), hepatitis, hyperglycemia, lymphadenopathy, muscle pain, and alopecia. Albendazole has fewer side effects, and mebendazole is well tolerated due to low absorption.

Piperazine leads to the opening of chlorine channels in nematode cell membranes, their hyperpolarization and para-lysis. The worms are then eliminated by intestinal peristalsis. Piperazine can be used to treat ascariasis and entero-biosis. 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 peristaltic movements of the intestines. 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 it causes dizziness and drowsiness.

Tapeworms (tapeworms, cestodes, flukes) are best treated ***with praziquantel*** . In addition to cestodes, praziquantel works very well on schistosomiasis. It increases the permeability of the worm's coat to calcium so that its musculature first contracts and then becomes paralyzed. After that, the disintegration of the shell and the death of the worm occur. For tapeworms, one dose of praziquantel (10 mg / kg) is applied ; if it is Taenia solium , in order to prevent cysticercosis , two hours after the administration of praziquantel, the patient should take a laxative (15 g M gSO_4) and expel the tapeworm from the digestive tract. For schistosomiasis, the dose is 20 mg / kg every 6 hours up to a total of 3 doses.

Praziquantel is well absorbed and penetrates into 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 (half-elimination time 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, as it caused vomiting more often than praziquantel, it also more often led to regurgitation of porcine intestinal tracts into the stomach and the formation of cysticercosis. That is why prazi-quantel has completely replaced it today. Niclosamide inhibits the creation of ATP in the processes of anaerobic metabolism. With such an action, niclosamide leads to the separation of the head of the tapeworm (scolex) from the intestinal wall, so intestinal peristalsis throws the entire tapeworm out. It does not destroy tapeworm eggs. Niclo-zamide 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, thereby reducing the creation of ATP in parasite cells. The drug is administered orally, and is eliminated in the urine. It can cause diarrhea, nausea, vomiting, headache. It rarely leads to tinnitus, insomnia and fever.

Filariasis (Filaria Loa Loa , Brygia malayi , Wuchereria ban - crofti) is treated ***with diethyl-carbamazine*** . This drug changes the surface of the microfilariae and makes them susceptible to the action of the host's immune system. It kills adult worms gradually. It also interferes with the creation of prostaglandins, which leads to vasoconstriction and difficult expansion of microfilariae. Penetrates into all tissues. Both the unchanged drug and its metabolites are excreted in the urine. Due to the sudden death of microfilaria, the so-called **Mazotti's** reaction: 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 micro-filariae go into the eye, onchocerciasis (Onchocerca volvulus), is treated with another drug, ivermectin. ***Ivermectin*** opens chlorine channels in microfilariae cells, which leads to membrane hyperpolarization and paralysis. This allows the immune system to remove the microfilariae. Thanks to the gradual action on the microfilariae, ivermectin does not lead to 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. And ivermectin can cause a Mazotti-like reaction due to the sudden death of large numbers of microfilariae.

Ivermectin is administered orally or subcutaneously. After absorption, most of the drug is eliminated through the bile. The semi-elimination time is 12 hours.

Side effects of ivermectin are mild: itching, fever and tenderness of the lymph nodes.

ANTISEPTICS AND DISINFECTANTS

Disinfection is the process of destroying the vegetative forms of microorganisms, while the spores remain undamaged. If disinfection is carried out on the skin and mucous membranes of a person, 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 for tissues to be applied systemically, so they are used only locally. According to their chemical composition, they can be classified into 10 groups:

I) **Alcohols**. The most used is ethanol (CH_3-CH_2OH) in a concentration of 70%. It is used to clean the skin before the injection and before the surgical intervention (then the skin is first cleaned with gasoline, then with alcohol and finally with an iodine preparation).

II) **Acids**. Boric acid (H_3BO_3) is used as a 3% solution for washing hollow organs (bladder, vagina , rectum). In powder form, it is used for sprinkling gauze on wounds infected with Pseudomonas aeruginosa.

III) **Phenols**. The first phenol used was ordinary phenol, known as carbolic acid (C_6H_5OH). The English surgeon Lister was the first to start the era of antisepsis (in 1864) 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 dilution of 1:5000 for washing wounds. Hydrogen peroxide ("hydrogen", H_2O_2) in the form of a 3% solution is used for washing wounds; it not only oxidizes microorganisms, but creates foam (due to the release of oxygen) that purely mechanically expels impurities from the wound. It also has a local hemostatic effect. Very deep wounds should not be flushed with hydrogen peroxide because the released oxygen can enter open blood vessels and cause gas embolism. In the case of threefold greater dilution (0.3%), hydrogen peroxide can be used to rinse the oral cavity and oropharynx with.

A compound of acetic acid with hydrogen peroxide (peracetic acid, CH_3-$COOOH$) is used to disinfect objects.

V) **Halogen compounds**. These are substances that have a halogen element in their molecule (usually iodine or chlorine). Alcoholic solution of iodine (tincture of iodine: 6.5 g of iodine + 2.5 g of potassium iodide + 91 g of concentrated alcohol) is used for cleaning the skin before surgical intervention, for coating the wound area and for quick preparation of the surgeon's hands. In recent times, compounds of iodine with polyvinyl-pyrrolidone, the so-called, are used to clean the skin. povidone-iodine, solution and foam. Care should be taken with iodine preparations in young children because excessive absorption from the skin can lead to hypothyroidism.

Carrel-Dakin's solution (sodium hypochlorite solution) is used for washing wounds. A chloramine solution (p-toluenesulfan chloramide sodium, 0.25-0.5%) has a similar function, which, in addition, can be used to disinfect the front of the goal and floors (1-5%).

VI) **Detergents**. Detergents are surface-active substances whose cationic part penetrates the membrane of microorganisms and destroys it. The cationic part almost always contains quaternary nitrogen. Benzalkonium chloride and other detergents are widely used to disinfect objects and floors.

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 the microorganism is an anion. Soaps are actually sodium or potassium salts of fatty acids. They are used for washing and disinfecting the skin before surgical intervention.

VIII) **Heavy metals**. Silver nitrate ($AgNO_3$) in a concentration of 0.1% (Krede's drops) was successfully used to prevent eye infections caused by gonorrhea; each newborn was instilled with one drop of this solution in both eyes. Silver nitrate sticks are used as a caustic agent to remove hypertrophic granulations in wounds .

Sublimate (mercuric chloride, $HgCl_2$) is used in a dilution of 1:1000 for disinfection of objects and, in the absence of better means, for rapid disinfection of surgeon's hands after washing. The mercury compound thimerosal (0.001-0.004%) is used as a preservative for vaccines and serums.

IX) **Colors**. Gentian violet is a natural dye that is used as a 1% solution for the treatment of resistant candidiasis of the oral cavity of newborns (thrush). Rivanol is an acridine dye that is used as a 0.1% solution for washing wounds.

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 in the form of a solution (2%) that must be alkalinized (pH around 8) in order to be activated.

IMMUNOMODULATORS (IMMUNOSUPPRESSANTS AND IMMUNOSTIMULATORS)

Medicines that reduce the activity of the immune system are called immunosuppressants. The need for immunosuppression occurs during tissue and organ transplantation (to avoid rejection) and when autoimmune diseases occur (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 the circulation (these are mainly T-lymphocytes) and the production of antibodies against a specific antigen. The synthesis of interleukins, especially interleukin 2, decreases. When it comes to transplantation, glucocorticoids have the most effect if they are administered from the beginning, before the immune response to the foreign tissue is even established. If the immune response is already established, their effect is much weaker, but it still exists. Side effects of corticosteroids are numerous (see chapter on hormones) after long-term use. Oral prednisolone 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. Unlike their application in the treatment of malignant tumors, where they are administered in large doses intermittently, with breaks, as immunosuppressants they are administered in small doses, continuously. Cyclophosphamide (an alkylating agent), azothioprine (a pro-drug, which is metabolized in the body to an active drug, an antimetabolite of mercaptopurine) and methotrexate (an antimetabolite, an analog of folic acid) are most often used.

Cyclophosphamide binds its active group (chloro-ethyl-amine) to nucleic bases in DNA and leads to errors during replication. Side effects are a consequence of its basic pharmacological effect: 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 and cell death occur during re-replication. Mercaptopurine also damages blood lines, leading to anemia, leukopenia and thrombocytopenia, and can damage the liver. Also, azathioprine is converted in the body into thioinosinic acid, which prevents 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. Half-elimination time is around 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 analogue that blocks dihydrofolate reductase, reduces the synthesis of tetrahydrofolic acid and interferes with the functioning of the enzyme whose cofactor is methyl-tetrahydrofolic acid. The most important enzyme from this group is thymidylate synthetase, whose blockade prevents the creation 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 kidney and heart transplant rejection in the first 6 months after surgery, often together with cyclosporine and corticosteroids, and to prevent and treat graft-versus-host reactions after hematopoietic stem

cell transplantation cell. It is currently more effective than all other immunosuppressants for this indication. Recently, mycophenolate mofetil is also used to treat rheumatoid arthritis, lupus nephritis and inflammatory bowel diseases. It leads to bone marrow damage and increases the incidence of skin and lymphatic tissue cancer. 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 one-week 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 lipid-soluble peptide antibiotic (cyclic peptide with 11 amino acids), blocks the differentiation of T-lymphocytes in the early stages of establishing an 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 it 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 bile (the dose is 15 mg / kg). However, it has a pronounced *nephrotoxic* effect, so urine and serum creatinine levels must be controlled during therapy. In addition, it causes hyperglycemia, hyperlipidemia, hirsutism and mild hepatitis. In the same group of antibiotics there is also a newer drug, ***tacrolimus*** **.** Its mechanism of action and side effects are similar to ciclosporin. It is used to prevent transplant rejection when other drugs fail, but also in other indications for which ciclosporin is used. It is administered intravenously or orally.

Mammalian rapamycin binding site inhibitors (mTOR inhibitors). The mammalian rapamycin binding site is a key element of a complex signaling system that regulates cell growth, metabolism, and proliferation. When this place is blocked, it will, among other things, block the stimulatory effect of cytokines on lymphocytes, which disturbs the work of the immune system. Medicines that block the binding site of rapamycin are sirolimus, temsirolimus and everolimus. ***Sirolimus*** is used alone or in combination with other immunosuppressants, for the prevention of acute transplant rejection and for the prevention and treatment of the "graft-versus-host" reaction 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 clogging of the stent. **Everolimus** is as effective as sirolimus, it just has better bioavailability. **Temsirolimus** is not used as an immunosuppressant. All rapamycin binding site inhibitors 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 thalidomide derivative that has the same effects, but less toxicity (it causes thrombosis less frequently, 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 acts nephro- and hepato-toxic. Antimalarial ***hydroxychloroquine*** is also useful in the treatment of rheumatoid arthritis , which raises the pH of intracellular organelles and thus interferes with the processing of antigens. 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 graft rejection, especially if corticosteroids have failed. Since T-lymphocytes are predominantly present in the blood, anti-lymphocyte globulin primarily suppresses cellular immunity. Adverse effects of these preparations are anaphylactic reaction, serum sickness and the occurrence of histiocytic lymphoma at the site of multiple globulin initiation.

Muromonab-(CD 3) is a monoclonal antibody obtained from the blood of mice, which binds to the CD 3 antigen on T lymphocytes. The consequence of the binding of muromonab to the CD 3 antigen is the inhibition of the activation of T lymphocytes, so that they 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). Adverse 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, during childbirth, the blood of the fetus and the blood of the mother may mix and sensitization of the mother to the Rh -factor, i.e. creation of 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 fetal erythroblastosis may occur. To prevent sensitization of the mother, she should receive anti- Rh globulin (of human origin) and . m . within 72 hours of giving birth. Antibodies against the Rh factor from this globulin coat the erythrocytes of the fetus that reach the mother's bloodstream and thus prevent sensitization.

Immunostimulators 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 deficiency 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 Giorgi syndrome (Di George ; aplasia of the thymus and lack of cellular immunity), where it leads to the maturation of T-lymphocyte precursors).

Interferons. There are three types of interferon: α, βand γ. Within the immune response, they perform many functions that are still insufficiently elucidated. Interferon αis used to treat hairy cell leukemia, Kaposi's sarcoma, and chronic hepatitis B and C. Adverse effects of interferon αare: flu-like syndrome, depression (with suicidal tendencies), granulocytopenia, cardiovascular disturbances (hypotension, hypertension, arrhythmias), nephrotoxicity and hepatotoxicity. Interferon β-1 b is used for the treatment of relapsing multiple sclerosis (only if the patient has at least 2 neurological deteriorations in the last 2 years) and interferon γfor the treatment of chronic granulomatous diseases. Adverse effects of interferon βare: 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 and 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 in patients with AIDS , kidney tumor or melanoma, with the simultaneous administration of lymphocytes and "killer" cells originating from the patient himself, which were previously kept in in vitro conditions, and exposed to interleukin 2. The effect of this kind of therapy is still modest. Adverse 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 the Dukes C stage (Dukes C ; the tumor has penetrated the colonic wall up 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 bacilli bovis. Their product is muramyl-dipeptide, which activates T-lymphocytes and natural "killer" cells. BCG vaccine is only useful if administered intravesically for the treatment of papillary bladder cancer. After instillation through the urinary catheter, it is left for two hours before urination. When using this medicine, a severe hypersensitivity reaction may occur.

Immunoglobulins can also be used as immunostimulators. If they are isolated from the plasma of ordinary blood donors, then we get 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 previously suffered from an infectious disease, or were vaccinated against it, then we

get a preparation with a high titer of antibodies against that infectious disease (the so-called hyperimmune globulin *)*. Gamma-globulin is given to patients with congenital deficiency of humoral immunity, and to patients with idiopathic thrombocytopenic purpura or with autoimmune hemolytic anemia. It has also been shown to be useful in the treatment of autoimmune diseases such as Kawasaki disease or Guillain-Barre syndrome. We give hyperimmune globulin to patients suffering from a severe form of an appropriate infectious disease or to bind toxins produced by microorganisms (eg tetanus toxin). The main adverse effects of immunoglobulin administration are anaphylactic reaction and hypotension.

MONOCLONAL ANTIBODIES

Monoclonal antibodies arise from a group of B lymphocytes (clones) that originate from the same cell, so that all antibodies are the same 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 immunized with the antigen) are fused with "rage-dead" plasmacytoma cells. The hybrid cells are then grown in cultures where they make monoclonal antibodies. A more modern way of producing monoclonal antibodies is through genetic engineering, where a bacteriophage carrying the gene for a monoclonal antibody is first selected, and then it infects cultures of Escherichiae coli, which further produces the desired monoclonal antibody.

Gene manipulation can make a monoclonal antibody that is " **chimeric** ", i.e. contains an antigen-specific part that is of murine origin and an antigen-nonspecific part (Fc fragment) that is of human origin. If an even larger part of the antibody of murine origin is replaced by fragments of human origin (as opposed 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, so they cause fewer allergic reactions. Below are the most important monoclonal antibodies that have been widely used for the treatment of various diseases.

- **alemtuzumab** (humanized antibody), binds to CD 52 on B -lymphocytic leukemia cells, for the treatment of which it is used;
- **cetuximab** (a chimeric antibody) binds to the epidermal growth factor receptor, and is used to treat head and neck and colon cancers;
- **bevacizumab**, a humanized antibody that binds to vascular endothelial growth factor - thus prevents angiogenesis and is used to treat metastatic colon cancer;
- **ofatumumab** is a human monoclonal antibody that binds to the CD 20 molecule on B lymphocytes, and is used to treat chronic lymphocytic leukemia;
- **rituximab** is a chimeric monoclonal antibody that binds to the CD 20 molecule on B lymphocytes (but second to ofatumumab) - used to treat non-Hodgkin's lymphoma, chronic lymphocytic leukemia and rheumatoid arthritis;
- **trastuzumab** is a humanized antibody that binds to the human epidermal growth factor receptor; used to treat breast cancer;
- **adalimumab** is a human antibody that binds to tumor necrosis factor alpha, so it 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, so it is used in the treatment of rheumatoid arthritis and Crohn's disease;
- **Etarnecept** is a protein complex consisting of the Fc fragment of a human antibody and tumor necrosis factor receptor alpha; it is used in the treatment of rheumatoid and other arthritis;
- **infliximab** is a chimeric antibody against tumor necrosis factor alpha, so it is used to treat rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis;

- **basiliximab** is a chimeric antibody that binds to CD 25, i.e. for interleukin 2 receptor; used for prophylaxis of acute kidney transplant rejection;
- **daclizumab** is a humanized antibody that binds to CD 25, i.e. for interleukin 2 receptor; used for prophylaxis of acute kidney transplant rejection;
- **natalizumab** is a humanized anti-integrin antibody, so it interferes with the adhesion of leukocytes and their exit into the tissue; it is used to treat multiple sclerosis and Crohn's disease;
- **omalizumab** is a humanized antibody against IgE antibodies, and is used to treat allergic asthma;
- **Tocilizumab** is a humanized antibody that binds to the interleukin 6 receptor; used to treat rheumatoid arthritis.

CHEMOTHERAPY OF MALIGNANT DISEASES

Chemotherapy of malignant diseases has advanced significantly in recent decades, so that today it is possible to cure even 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 normal and malignant cells.

The life cycle of normal and malignant cells takes place in 4 phases. In the first phase, which is denoted by G_1, the cell prepares for the replication of its DNA , by synthesizing all the necessary enzymes for that process. In the next, S phase, DNA replication takes place, and then the G_2 phase occurs, in which all necessary enzymes and other molecules for mitosis are synthesized, i.e. definitive division into two cells. In mitosis, the chromosomes condense, separate and definitively divide the mother cell into two daughter cells.

Some cells continuously re-enter this cycle of division, while others enter a resting phase, denoted by G_0. From the resting phase, only some cells can subsequently "wake up" and start dividing again. We call such cells ***stem*** cells cells). All three types of cells are present in tumors: definitively differentiated, continuously dividing cells, 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-nonspecific cytostatics (eg, alkylating agents); cytostatics that act only in one phase of the cell cycle (eg vincristine and vinblastine that act only in mitosis) are called cycle- or phase-specific drugs. In the case of non-cycle-specific drugs, the dose-response function is linear, i.e. as the dose increases, the number of malignant cells killed also increases. Code cycle - ie. phase-specific drugs, this function has a plateau, i.e. a steady increase in dose after some 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 speed 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 the tumor's vascularization is compromised and its cells die more and more. Since the organism is

not able to deal with malignant cells on its own, as it can with microorganisms, the complete destruction of all malignant cells must be achieved with the use of cytostatics. That's why cytostatics are usually used in combinations, and pulsed, that is. high doses are given in shorter time intervals, and then a break of about 3-4 weeks is allowed, in order for the patient to recover from the 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 applied, cytostatics with different mechanisms of action and different types of side effects are always used, in order to achieve the greatest possible effect with as little toxic effect on the patient's body as possible.

It is extremely important to apply appropriate doses of cytostatics: the use of smaller than recommended doses significantly reduces the effect of the drug on the tumor, while the use of larger doses leads to unacceptable toxic effects on the patient's body.

Resistance of malignant cells to cytostatics

There are several mechanisms of resistance of malignant cells to cytostatics. The basic form of resistance is a direct consequence of the phase in which the cell is located. 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 of the emergence of resistance is the localization of cells in areas where drugs cannot reach (eg in the subarachnoid cerebrospinal space). Then the cells simply do not react to cytostatics, because they do not come into contact with them.

However, the so-called has greater importance. **acquired** resistance, i.e. resistance as a consequence of tumor exposure to cytostatics. It is usually characterized by crossbreeding, i.e. after exposure to one drug, tumor cells become resistant to the entire group of cytostatics, which also includes the administered drug. The most common mechanism of this form of resistance is excessive expression of the gene encoding ***the transmembrane glycoprotein P.*** Glycoprotein P is actually a transmembrane pump that normally expels exogenous or endogenous toxins from the cell. Normally, this pump is found in the cells of the renal tubules, the epithelium of the jejunum and colon, the epithelium of the biliary tract, and the capillaries of the brain and testis. In tumors that are exposed to the action of cytostatics, the expression of this pump is induced, as a result of which tumor cells very quickly and easily expel cytostatics, before they exert an effect on functional molecules.

This kind of resistance, where there is a huge expression of glycoprotein P , is especially common when using the following cytostatics: anthracycline antibiotics, vincristine and vinblastine, paclitaxel, etoposide, mitomycin and plicamycin. It should be known that if resistance occurs to one of these cytostatics, resistance to all of them practically arises.

According to the site of action and chemical structure, cytostatics can be classified into several groups:

Alkylating agents
Antimetabolites
Antibiotics
Plant alkaloids
Enzymes
Hormones
The others.

Alkylating agents

In their molecule, these substances have alkyl radicals, which easily bind to nitrogen atoms in purine and pyrimidine bases of nucleic acids. They are most often attached to ***the nitrogen at position 7*** in the purine nucleus (guanine). The consequence of guanine alkylation can be cross-linking of 2 DNA strands , or incorrect base pairing (guanine is paired with thymidine instead of cytosine). DNA strand breaks and cell death can also occur .

Alkylating agents act on cells at all stages of their life cycle. That is why, 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 (G_0). The most important groups of alkylating agents are: nitrogen blisters, nitrosoureas, alkyl sulfonates , ethyleneimines and triazenes.

Nitrogen blisters. The most important representatives of this sub-group are mechloretamine, cyclophosphamide, ifosfamide, chlorambucil and melphalan. Mechlorethamine was **the first** cytostatic to enter general use. It was obtained as *a derivative of sulfur blister war poison* in the 1940s. It contains a reactive cyclic *ethyleneammonium ion* . It stays in the body for a very short time (the half-elimination time is about 10 minutes), it 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 MO PP protocol.

Cyclophosphamide has the widest spectrum of action of all alkylating agents. After oral or parenteral administration, cyclophosphamide is converted into the active metabolites phosphoramide and acrolein by the cytochrome P 450 system. While cyclophosphamide is 15% bound to plasma proteins, its metabolites are even 50% bound to the same proteins. Both cyclophosphamide and its metabolites are excreted in the urine, where they irritate the mucous membrane of the urinary bladder, causing *haemorrhagic cystitis* . Large doses of cyclophosphamide can lead to a weakening of water excretion in the kidneys, and thus to *hyponatremia* .

Ifosfamide behaves in the body similarly to cyclo-phosphamide; and it is converted into an active metabolite. It works better than cyclophosphamide on germ cell carcinomas and sarcomas. Like cyclophosphamide, ifosfamide causes hemorrhagic cystitis; in order to prevent this unwanted effect, ***mesna*** , a substance with thiol (SH) groups, which binds to the cytostatic and its metabolites in the urine, is used along with ifo-sfamide , making it impossible to bind to cells of the transitional epithelium.

Chlorambucil is a substance with a benzene ring, which is used as a palliative therapy for chronic hematological malignancies (eg chronic lymphocytic leukemia). Melphalan is an amino acid derivative of mechlorethamine. It is used in the palliative therapy of ovarian cancer, breast cancer or multiple myeloma.

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 reach high concentrations there. On the other hand, they are very chemically unstable, and are easily broken down into chloroethyl diazohydroxide and isocyanate ($T_{1/2}$ = 10 minutes), active metabolites that perform both alkylation and carbamoylation of tumor cell DNA . Due to rapid degradation, these drugs cannot be administered orally. They are used to treat primary brain tumors (astrocytomas, oligodendrogliomas). Their characteristic side effect is pulmonary fibrosis.

Streptozocin , a water-soluble substance, belongs to nitrosoureas . It selectively leads to a deficiency of nicotinamide adenine dinucleotide (NAD) in pancreatic islet cells . That is why it is used to treat pancreatic beta-cell tumors (non-sidioblastomas). It is administered only intravenously, and it breaks down quickly ($T_{1/2}$ = 10 minutes). It can damage *kidney tubules* .

Temozolomide is another alkylating agent that penetrates the central nervous system very well. It is used to treat *primary brain tumors,* and its effectiveness 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 that is used in practice is busulfan . It is administered orally; it is well absorbed, but it breaks down quickly ($T_{1/2}$ = 5 minutes), so the metabolites are excreted in the urine. It is used for palliative treatment *of chronic myeloid leukemia* .

Ethyleneimines . The representative of this group that is used clinically is thiotepa . This drug is *directly introduced into the urinary bladder* through a urethral catheter, for the treatment of multifocal bladder cancer.

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 ($T_{1/2}$ = 19 minutes), then metabolized and eliminated ($T_{1/2}$ = 5 hours) by tubular secretion. It is the best drug for fighting *meta-static melanoma* (remission in 20% of patients), and is also used for sarcomas and Hodgkin's disease.

Antimetabolites

Antimetabolites are structural analogs of natural molecules that participate in the synthesis of DNA and RNA . They work by competing with natural molecules for active sites on enzymes, or simply completely replacing natural molecules in the synthesis process. That is why they are most active in the S -phase, and practically do not act on 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 mostly 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 into 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 further from it, N^{5} , N^{10} - 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 50% of it binds to plasma proteins. The elimination is done in 3 phases: first distribution, initial and late elimination phase. The drug is excreted through the kidneys, glomerular filtration and tubular secretion.

It is interesting that methotrexate accumulates in tumor cells in the form of a polyglutamate conjugate, 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 applied intrathecally (into the subarachnoid space), to prevent the occurrence of meningeal metastases in acute lymphoblastic leukemia.

A specific acute adverse 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 using *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 for refractory T-cell lymphoma. Pemetrexed and pralatrexate are administered together with folic acid and vitamin B_{12}, in order to prevent a toxic effect on the bone marrow.

Thioguanine . Thioguanine is a pro-drug, which is converted into thioguanosine monophosphate under the action of hypoxanthine guanine-phosphoribosyltransferase (HGPRTase). That substance further turns into thioguanosine triphosphate, the active form of the drug, which is incorporated into DNA or RNA , and leads to *incorrect coding* of proteins. Thioguanine is slowly absorbed; it is metabolized in the liver, and the metabolites are excreted in the urine (about 40% of the ingested drug is excreted in 24 hours). It works best on *acute myeloid leukemia* .

Mercaptopurine . The mechanism of action of mercaptopurine is very similar to that of thioguanine; and it must be activated under the action of 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 under the action of the enzyme xanthine oxidase. The semi-elimination time is only about 20 minutes. Mercaptopurine is used for the treatment of *acute leukemias* , primarily lymphoblastic.

Fludarabine is related to the antiviral drug vidarabine. In cells, it is transformed into the active metabolite 2-fluoro-ara-adenosine triphosphate, which inhibits DNA polymerase, a key enzyme in DNA synthesis . It is used for the treatment of *chronic lymphocytic leukemia* .

Pentostatin inhibits the enzyme ***adenosine deaminase*** , which participates in the breakdown of adenosine. Due to the blockade of that enzyme, adenosine and deoxyadenosine triphosphate accumulate, which have a toxic effect on lymphocytes. Pentostatin is very effective in the treatment of *hairy cell leukemia* (remissions in 90% of patients). **Cladribine** is also used for the same purpose .

Gemcitabine is transformed in cells into the active metabolite difluoro-deoxycytidine triphosphate, which interferes with DNA synthesis . It is used in intravenous infusion for the treatment *of pancreatic cancer* that has metastasized, as well as for microcellular lung cancer.

Cytarabine, after converting to the triphosphate form, inhibits the DNA polymerase of tumor cells. It is active against acute myeloid leukemia. It is administered intravenously, and it is rapidly metabolized ($T_{1/2}$ = 10 minutes) to uracil arabinoside, which is excreted in the urine.

Fluorouracil (5-fluorouracil) is transformed in tumor cells into the active metabolite 5-fluoro-2`deoxyuridine- S` -phosphate, which then inhibits ***thymidylate synthetase*** , an enzyme that synthesizes thymidylate (dTMP), necessary for the creation of DNA . In that reaction, the cofactor is *folinic acid* , which enhances the action of fluorouracil. Fluorouracil is administered intravenously, and is rapidly metabolized in the liver ($T_{1/2}$ = 10 minutes); only 20% of the drug is excreted through urine.

Fluorouracil is primarily used to treat breast and gastrointestinal cancers. In the form of a cream, it is used locally for the treatment of premalignant keratoses of the skin.

Capecitabine is an oral prodrug, which is converted to 5-fluorouracil in cells. It is used, like fluorouracil, for the treatment of breast cancer and metastatic colon cancer, but only when patients have not responded to classical therapy. A number of patients who receive this medicine develop a painful, red rash on the palms and soles.

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 functioning.

Antitumor antibiotics

These drugs were named antibiotics, because they were discovered in nature as products of microorganisms, which they use to defend themselves against other beings. Antibiotics are interposed (***intercalated) between two adjacent*** DNA bases (especially between guanine and cytosine, and guanine and thymine), which prevents further 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 Streptomyces bacteria peucetius . While daunorubicin has a favorable effect only on *acute leukemias* , doxorubicin has a very *broad spectrum* of action on various malignant tumors. Doxorubicin is therefore incomparably more used in practice. Since it has the ability to create free radicals, doxorubicin exhibits specific *cardiotoxicity* (arrhythmias, negative inotropic effect), and can again cause an inflammatory reaction in places that were previously exposed to ionizing radiation . recall " reaction). Due to its distinctly red color, the urine of patients who receive it will be reddish, and there may be hyperpigmentation of the nail bed, as well as skin folds.

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 absence of one methoxy group. In everything, it is similar to doxorubicin, except that it is more lipophilic and somewhat stronger.

Bleomycin is a glycopeptide antibiotic, which is very effective against advanced testicular cancer. It is administered parenterally. Bleomycin inactivates the enzyme bleomycin hydrolase, which is found in almost all tissues except the lungs and skin. That's why bleomycin exhibits serious side effects in those tissues (***lung fibrosis*** , skin thickening, hyperpigmentation). Many patients react with an elevated body temperature to the use of bleomycin.

mitomycin is activated by the reduction process. It is administered intravenously, and does not penetrate the central nervous system. It is used in the palliative therapy of cancer of the stomach, pancreas and colon.

Dactinomycin is an antibiotic active against tumors in children: Wilms' tumor, Ewing's sarcoma and rhabdomyosarcoma.

Plicamycin (mithramycin) is generally not used to suppress malignant tumors, but to treat severe hypercalcemia. It has the unique property of inhibiting bone resorption, thus 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.

Vinca rosea alkaloids (**vincristine, vinblastine and vinorelbine**) work by binding to *tubulin* , a protein that builds microtubules, and preventing its incorporation into the mitotic spindle. In this way, they ***prevent the mitosis*** of malignant cells, and thus the growth of tumors. These drugs are metabolised in the liver and excreted in the bile. Vincristine is used to treat acute lymphoblastic leukemia, Hodgkin's and non-Hodgkin's lymphomas, and solid tumors in children. Vinblastine successfully acts on testicular cancer, and vinorelbine on known-predominant non-small cell lung cancer. Vincristine specifically causes ***neuropathy*** (because microtubules are also needed for axonal transport).

Etoposide and teniposide are toxins from the plant *Podophyllum peltatum* that inhibit the enzyme topoisomerase II, which prevents the synthesis of DNA and thus the division of malignant cells. Etoposide works well on *testicular and ovarian germ cell tumors* , lymphoma, microcellular lung cancer and acute leukemia. Teniposide is most useful in the treatment of acute lymphoblastic *leukemia* .

Paclitaxel and docetaxel are semi-synthetic derivatives of natural substances from the *Taxus baccata plant* , which also interfere with the functioning of the mitotic spindle, but by a slightly different mechanism than the alkaloids from the Vinca rosea plant. In addition, they induce apoptosis of malignant cells. Paclitaxel is primarily metabolized in the liver; a very small amount of the drug is excreted in the urine. Both drugs are active against breast, lung, ovarian and head and neck cancers. Specific toxicity is reflected in the occurrence of ***peripheral neuropathy*** .

The alkaloid camptothecin was isolated from the plant *Camptotheca acuminata* , whose semi-synthetic derivatives **irinotecan** and **topotecan** inhibit topoisomerase I, thus preventing DNA replication in malignant cells. Topotecan is used to treat advanced *ovarian cancer* , and irinotecan to treat metastatic *colon cancer* .

Enzymes

L-asparaginase is an enzyme of bacterial origin, which breaks down l-asparagine into aspartate and ammonium. When administered intravenously to a patient, it remains in the bloodstream and leads to asparagine deficiency. Because *acute lymphoblastic leukemia cells* cannot synthesize asparagine on their own and depend on asparagine from the blood, they are left without this amino acid, and cannot divide.

After the infusion, the drug remains in the blood for a day or two. It is gradually degraded by serum proteases and phagocytized by the cells of the reticulo-endothelial 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 does not have a toxic effect on the bone marrow, so it can be combined with other cytostatics.

Hormones

Tumors whose growth depends on the effect of hormones can be quite successfully affected by drugs that bind to hormone receptors (most often they block them, and sometimes they overactivate them). The most important in this group are drugs that bind to sex hormone receptors.

Tamoxifen blocks estrogen receptors, so it can prevent the growth of breast cancer whose cells have such receptors. Tamoxifen is slowly absorbed after oral administration, and is concentrated in tissues that have estrogen receptors (breasts, ovaries, uterus). It is metabolized in the liver through the processes of hydroxylation and glucuronidation, and the resulting metabolites are excreted through the bile.

Tamoxifen leads to remission of breast cancer whose cells *have estrogen receptors* in 60% of patients. The effect lasts for about a year, and for about 10% of women, even several years. It is used as an additional (adjuvant) therapy in menopausal patients, whose tumor has been surgically removed. The drug is well

tolerated; causes hot flashes (feeling of heat in the face and neck accompanied by reddening of the skin) in 15% of patients, and sometimes vaginal dryness. Rarely, bone pain accompanied by hypercalcemia occurs.

Aromatase is an enzyme that converts androgens originating from the adrenal gland into estrogens in adipose tissue. Thanks to this enzyme, women in menopause have sufficient amounts of estrogen, even though the ovaries have stopped functioning. Aromatase inhibitors (**anastrozole, letrozole, exemestane**) can prevent or slow down 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 of moderate severity: acceleration of osteoporosis, increase of lipids in the plasma, pain and stiffness of the joints.

The latest anti-estrogen used in oncology is **fulvestrant**, which can cause the downregulation of estrogenic receptors, i.e. to *reduce their number*. It is used as a depot intramuscular injection, once a month, in metastatic breast cancer whose cells have estrogen receptors.

Flutamide blocks *the receptors for androgen* hormones. It is administered orally, and is used to treat prostate cancer. It is particularly useful in combination with the gonadotropin-releasing hormone agonist, leuprolide. At the beginning of therapy, leuprolide temporarily leads to an increase in testosterone secretion, so flutamide successfully eliminates this unwanted phenomenon. Flutamide causes hot flashes and impotence.

Estramustine is *a hybrid* molecule, made of estradiol and nitrogen blister. 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 analogs of gonadotropin-releasing hormone from the hypothalamus. When administered continuously, they prevent the release of gonadotropin from the pituitary gland, effectively leading to chemical castration. They are used for palliative treatment of prostate cancer. They are well tolerated, they only cause hot flashes.

The somatostatin analog **octreotide** is a peptide that can *inhibit the secretion* of insulin, glucagon and hormones from carcinoid cells. That is why it is used for the treatment of metastatic carcinoid tumors and carcinoma of the islets of Langerhans of the pancreas. It is applied parenterally, and it stays in the body for a relatively short time (but significantly longer than somatostatin; $T_{1/2}$ = 1.5 hours). It is excreted through urine. As a side effect, it can cause hypoglycemia or hyperglycemia.

Other cytostatics

Hydroxyurea inhibits the conversion of ribonucleotides into deoxyribonucleotides, thereby preventing DNA synthesis. It is administered orally, quickly absorbed, and eliminated largely unchanged through the kidneys ($T_{1/2}$ = 2-3 hours). Hydroxyurea is used in the treatment *of chronic myeloid leukemia*, both in induction and maintenance of remission. After prolonged use, it causes hyperpigmentation and hyperkeratosis.

Procarbazine spontaneously oxidizes, creating free radicals that damage DNA. It also methylates guanine at position N 7. The drug is quickly and well absorbed after oral administration, and then metabolized in the liver. Drug metabolites are excreted in the urine ($T_{1/2}$ = 10 minutes). It penetrates well through the hemato-encephalic barrier. It is used in the combined therapy of Hodgkin's and non-Hodgkin's lymphomas, as well as for microcellular lung cancer.

Procarbazine has a high potential to interact *with* other drugs. It potentiates the depressant effect of sedatives, and when used with alcohol, it can cause a similar reaction as disulfiram. If used together with foods rich in tyramine or with sympathomimetics, it can lead to a spike in blood pressure.

Mitotane is a drug that, after oral administration and partial absorption, shows a tendency to accumulate in fatty tissue, especially in the cortex of the adrenal gland. When enough accumulates, 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 the synthesis of DNA and RNA in *ovarian* adenocarcinoma cells , by a still insufficiently known mechanism. After oral administration, it is well absorbed, it is metabolized in the liver and the metabolites are excreted in the urine.

Cisplatin is an inorganic platinum complex that binds to the N 7 position of guanine and results in cross-linking of two nucleic bases, similar to alkylating agents. The end result is interference with DNA replication . Cisplatin is particularly active against *testicular and ovarian cancer*. This drug remains in the human body for several days after intravenous infusion, because elimination through the kidneys is slow. Since it is eliminated through the kidneys, it concentrates there and can *damage the kidney tubules*. It also accumulates in the peri-lymph of the inner ear, leading to *hearing loss* at high frequencies. Peripheral neuropathy was also noted.

Carboplatin is *an analogue of cisplatin*, which is eliminated from the body much faster. Because of its faster elimination, its toxic effects on the kidney, inner ear, and peripheral nerves are significantly ***less*** than those 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 and interferes with its function. It is active against leukemia, lymphoma and breast cancer.

DNA topoisomerases I and II

DNA topoisomerases are enzymes that regulate super-coiling of human DNA . *Topoisomerase And* it participates in that process by breaking one strand of DNA , leading to the bending of the entire DNA , and then repairing the broken place. *T opoisomerase II* breaks both strands of DNA , causes the DNA to bend , and then rejoins both strands.

DNA replication and RNA transcription , because they actually enable the unwinding of DNA and access to other enzymes necessary for those two processes. The counterpart of human topoisomerases in the bacterial cell is the enzyme *gyrase* .

Recently, two more topoisomerases, designated as topoisomerase III and IV , have been discovered . Topoisomerase III is considered to have a significant role in the recombination process, while topoisomerase IV allows separation 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*** against specific proteins on the membrane of malignant cells. **Alemtuzumab is used** to treat beta-cell chronic lymphocytic leukemia, which carries the CD 52 antigen . It is a monoclonal antibody that binds to the CD 52 antigen and leads to the lysis of malignant cells. The monoclonal antibody **rituximab is used** for the treatment of follicular non-Hodgkin's lymphomas, whose cells carry the CD 20 antigen . Both alemtuzumab and rituximab are used only in patients who have previously been treated with cytostatics and did not respond well to them. **Trastu-zumab** is a humanized monoclonal antibody that binds to the HEP -2 antigen on the surface of breast tumor cells. It has recently been shown that early application of this antibody (already after breast removal) can significantly improve the prognosis of patients, i.e. to prolong survival.

Adverse effects of alemtuzumab are numerous and serious: neutropenia, anemia, thrombocytopenia, lymphopenia, increased frequency of infections (that is why patients receive antibiotic prophylaxis) and a *flu-like condition* during the administration of the drug.

Alemtuzumab is used as an intravenous infusion, three times a week, for a total of 12 weeks.

Adverse 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. And rituximab is 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 therapy 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 supply 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 anti-angiogenic effect, in some patients it can *make wound healing more difficult*, and lead to bleeding or intestinal perforation.

Cetuximab and panitumumab are monoclonal antibodies that bind to the epidermal growth factor receptor on malignant cells, block it, and thus stop tumor growth. They are used to treat head and neck cancer, and metastatic colorectal cancer that has the K RAS form of the RAS protein, a mediator of cell proliferation and differentiation.

Pembrolizumab is a humanized monoclonal antibody that binds to PD-1, the programmed death receptor on T-lymphocytes, and prevents PD-L1 and PD-L2 ligands from binding to that receptor. These ligands are normally produced by tumor cells, which in this way lead to apoptosis of T-lymphocytes and weakening of the immune response. Pembrolizumab prevents this immunosuppressive effect of the tumor, thereby preventing its spread, i.e. metastasizing. 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's 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 been operated on for colon cancer, it significantly prolongs survival. It causes loss of appetite and a flu-like syndrome.

Interferon alfa-2 b has shown a remarkable effect in hairy cell leukemia, where it induces remission in about 70% of patients. As an unwanted effect, it causes an elevated temperature and a flu-like syndrome.

Interleukins also have their place in the treatment of malignant tumors. **Aldesleukin** is a human recombinant inter-leukin 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 cause remission in about 15% of patients with renal cell carcinoma. At the same time, aldesleukin is very toxic, because it can cause **a syndrome of increased capillary permeability** , with hypotension, lung edema and increased heart load.

Thalidomide was widely used as a sedative in the sixties of the 20th century, but its use was then abruptly discontinued due to its teratogenic effect. A large percentage of children of mothers who used thalidomide during pregnancy developed **phocomelia**, a congenital anomaly in which the limbs are completely stunted. It was the inhibitory effect of thalidomide on the formation of new blood vessels (angiogenesis) that led to focomelia. In addition to inhibiting angiogenesis, thalidomide also has strong anti-inflammatory and immunomodulatory effects. A few years ago, the positive effect of thalidomide was observed in certain tumors, so today it is used for the *treatment of multiple myeloma*, usually together with dexamethasone. Thallidomide is highly toxic; in addition to the teratogenic effect, it causes peripheral neuropathy, hypothyroidism and increases the risk of deep vein thrombosis. That's why some of the oral anticoagulants are prescribed along with thalidomide. In the search for equally effective and less toxic drugs, derivatives of thalidomide were synthesized that retain the immunomodulatory effect, such as ***lenalidomide***. It is successfully used in the treatment of myelodysplastic syndrome, in patients with 5 q 31 deletion.

NEW DRUGS AGAINST MALIGNANT DISEASES

Inhibitors tyrosine kinases

Imatinib is a blocker of the abnormal enzyme tyrosine kinase, which is produced in chronic myeloid leukemia cells. This type of leukemia has an abnormal chromosome 22 that was created by the 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 treatment with interferon alfa. It is very effective: it leads to complete remission in as many as 88% of patients, and in 30% cells with the Philadelphia chromosome are lost (cytogenetic remission).

This drug also works well in gastrointestinal stromal sarcoma, whose cells contain abnormal tyrosine kinase. This type of tumor normally does not respond to other forms of therapy.

Imatinib is well tolerated. Adverse effects are: nausea, vomiting, edema, cramps, muscle pain, fever and fatigue. Neutropenia, thrombocytopenia and liver damage occur rarely.

Imatinib is administered orally and is well absorbed. It is metabolized in the liver via the CYP3A4 cytochrome P 450 isoform, and 25% of the drug is excreted unchanged in the urine. **Nilotinib and dasatinib** work by the same mechanism as imatinib, so they are used for the same indications.

Gefitinib and **erlotinib** inhibit tyrosine kinase, which is actually the intracellular part of the transmembrane receptor for epidermal growth factor (rEFR). They can lead to the remission of advanced lung cancer, provided that its membrane cells have rEFR. Bronchoalveolar carcinoma, which exhibits a particularly large number of rEFR, responds particularly well to these drugs. Both drugs are well tolerated; they only cause smallpox and diarrhea.

Sunitinib and pazopanib are tyrosine kinase inhibitors of vascular endothelial growth factor and platelet-derived growth factor, which are used to treat locally advanced or metastatic renal cell carcinoma. They lead to redness and blisters on the palms and soles, as well as anemia, leukopenia and thrombocytopenia.

Sorafenib inhibits serine/threonine and tyrosine kinase. It is used to treat hepatocellular carcinoma and renal cell carcinoma.

Inhibitors proteasome

Proteasomes are complexes of proteases in the cytoplasm of the cell, *tubular in* shape, which degrade proteins that have performed their function or are damaged. All the proteins labeled with one small peptide, called ***ubiquitin, enter these tubes***, and these are precisely the proteins that have performed their function or are damaged. After entering the tubules, the labeled proteins are broken down into amino acids. With the help of the proteasome, the cell gets rid of unnecessary proteins.

Bortezomib inhibits the proteasomes of malignant cells, so that there is an accumulation of unnecessary proteins in them and disruption of normal functions, i.e. malignant cell death occurs. It is used to treat multiple myeloma that has not responded to at least two types of therapy. Bortezomib may cause peripheral neuropathy, bone marrow suppression, and hypersensitivity reactions.

Derivatives vitamin A

Tretinoin accelerates *the differentiation* and reduces the proliferation of acute promyelocytic leukemia cells, thus improving the general condition of patients with this disease. It is used together with drugs that act cytolytically on the mentioned cells, such as **arsenic trioxide**. Arsenic trioxide induces remission in 70% of patients with acute promyelocytic leukemia, which has not responded to other types of therapy.

Another derivative of vitamin A, **bexarotene**, selectively activates the retinoid "ix" receptor, and thus reduces the proliferation of *T-cell skin lymphoma cells* (eg, mycosis fungoides).

Antibodies bound with cytostatics or broadcasters ionizing radiation

This type of therapy represents the so-called "targeted" pharmacological therapy, where the antibody binds to a defined place on the malignant cell, which is then acted upon by the "deadly load" that the antibody carries (toxin, cytostatic or radio-emitter).

Ibritumomab tiuxetan is an antibody that binds to the CD 20 antigen on non-Hodgkin's 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 CD 20 antigen, and which carries radioactive iodine 131. It is also used to treat non-Hodgkin's lymphoma, and exhibits the same side effects as ibritumomab tiuxetan.

Denileukin diphtitox is not an antibody, but *a hybrid protein* composed of part of diphtheria toxin and part of inter-leukin 2. It binds to cells that have a receptor for inter-leukin 2 (CD 25), and kills them in the same way as diphtheria toxin. It is used for the treatment *of cutaneous T-cell lymphomas,* resistant to standard therapy, whose cells have the CD D25 receptor. Denileukin diphtitox can cause allergic reactions and delayed edema of the lungs and extremities.

Gemtuzumab ozogamicin is an antibody that binds to the CD 33 antigen, and carries the antitumor antibiotic ***calicheamicin.*** It is used to treat patients over the age of 60 who have relapsed *acute myelogenous leukemia* , provided that the cells express the CD 33 antigen. Gemtuzumab ozo-gamicin causes bone marrow suppression and IV infusion reactions.

Unwanted actions cytostatics

Due to their mechanism of action, cytostatics have significant adverse effects on all tissues in the human body that divide rapidly. They actually act on these tissues as they do on tumors: they cause the death of a number of cells. In addition, they also have certain specific side effects, which are characteristic of each cytostatic agent. A good knowledge of the side effects of cytostatics is a prerequisite for their correct application. It is especially important that general practitioners know the side effects of cytostatics, so that they can recognize them in time in their patients and respond appropriately.

Nausea and vomiting occur very often with the use of cytostatics. They can be *anticipatory* in nature (occurring before receiving 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 during the application of cytostatics with a lower emetogenic potential, domperidone or one of the phenothiazines is used, at the latest one hour before the start of cytostatic administration, and continues with its application up to 24 hours after the application of chemotherapy. If the vomiting is anticipatory, lorazepam is indicated, and if the vomiting is delayed, it should be given with domperidone and dexamethasone.

If cytostatics with high emetogenic potential are used, the drugs of choice to prevent vomiting are 5 HT_3 serotonin receptor blockers: **ondansetron, granisetron, dolasetron and palonosetron** . Ondansetron is given parenterally (32 mg before chemotherapy, then the same dose is repeated after 24 hours) or orally (8 mg every 8 hours). 5 $HT_{3\ receptor}$ blockers are more effective if given together with dexamethasone (6-10 mg before chemotherapy).

When using cisplatin and other most emetogenic cytostatics, a *neurokinin-1 receptor blocker is added to the combination of the 5* HT_3 receptor blocker and dexamethasone. **aprepitant** , through which it acts in the organism with P. The medicine is applied for a total of three days, starting from the moment immediately before the rhyming chemotherapy.

Bone marrow suppression is a side effect of all cytostatics except vincristine and bleomycin. Anemia manifests itself only after several cycles of chemotherapy, due to the long life of erythrocytes in peripheral blood (about 120 days). In contrast, leukopenia peaks 7 to 10 days after the administration of cytostatics, and it takes about 20 days for 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 1×10^9 / L and the patient has a high temperature, then most likely an infection has occurred, so the use of antibiotics with a wide spectrum of action is advised. For milder infections, a combination of ciprofloxacin (orally) and amoxicillin with clavulanic acid (orally) is used, and for more severe infections, cephalosporins of the 3rd or 4th generation are given parenterally. In 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 enhances the functioning of mature granulocytes. An unwanted effect of these growth factors is ***pain in the bones*** , 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 mucous membrane of the oral cavity with the appearance of ulcers most often occurs with the use of methotrexate, fluorouracil and anthracycline. It can be prevented by good hygiene of the oral cavity and by sucking on pieces of ice during the infusion of fluorouracil. When using methotrexate, inflammation of the mucous membrane of the oral cavity can be shortened and alleviated by the use of folinic acid. Special preparations that cover ulcerations are also used.

Hyperuricemia occurs as a complication of leukemia and lymphoma treatment, due to the large production of uric acid. It can be prevented by adequate hydration of the patient and the use of allopurinol, starting one day before the application of cytostatics. Allopurinol inhibits the enzyme xanthine oxidase and thus prevents the formation 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 urate oxidase enzyme that oxidizes uric acid into more soluble compounds. Urate oxidase does not exist in the human body, but some other mammals possess it. Used in chemotherapy patients, rasburicase effectively reduces the concentration of uric acid.

Rasburicase is given once a day, in the form of an intravenous infusion, for 6-7 days. The half-life of rasburicase is 20 hours; it is degraded by numerous peptidases.

Unwanted effects of rasburicase are: allergic reactions, fever, nausea and vomiting. It must 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 must not be used during pregnancy, especially in the first trimester. They also **reduce the fertility of men and shorten the reproductive life of women** . However, no increased frequency of abortions or congenital anomalies was observed in pregnancies that occurred after the use of cytostatics.

Cardiotoxicity implies direct damage to myocardial cells by cytostatics. Not all cytostatics have a significant cardiotoxic effect, but some stand out for that: anthracyclines (doxorubicin and daunorubicin). Toxic effects can be acute or chronic. Acute toxic effects occur after bolus injections of anthracyclines, and are manifested as supraventricular tachycardias, reduction of T-waves in EKG or appearance of ventricular extrasystoles. Chronic toxic effects appear after a latent period of several months and manifest as cardiomyopathy with heart failure. Cardiomyopathy occurs especially often if the patient received more than 550 mg / m^2 of anthracycline.

Myocardial damage that occurs after the use of anthra-cycline is not reversible, and is based on damage to the mitochondria of heart muscle cells.

The cardiotoxicity of anthracycline preparations can be reduced in two ways. First, anthracyclines can be prepared as liposomal preparations, i.e. drug molecules are surrounded by a lipid membrane that prevents contact with tissues that are not the target of therapy. It has been observed that the application of liposomal preparations of cytostatics carries generally less toxicity. Second, before and during the administration of anthracycline, the patient can be given the drug ***dexrazoxane*** (a derivative of ethylenediamine-tetraacetic acid, E D TA), which prevents the oxidative and direct toxic action of cytostatics on mitochondria. Dexrazoxane is given in a 10:1 ratio with doxorubicin (eg 250 mg dexrazoxane to 25 mg doxorubicin).

Toxic action on the urinary tract is characteristic of cisplatin, cyclophosphamide and ifosfamide. Cisplatin primarily damages kidney tubules, while cyclophosphamide and ifo-spamide damage both kidney tubules and bladder epithelium, causing hemorrhagic cystitis. Hemorrhagic cystitis is a consequence of accumulation in the urinary bladder of acrolein, a metabolite of cyclophosphamide and ifosfamide. In addition, cyclophosphamide and ifosfamide lead to hyponatremia, because they increase the reabsorption of water in the collecting ducts 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 kidney tubules increases. Infusion of 2.5 L of saline over 12 hours

is recommended. In addition, the simultaneous application of ***amifostine thiol ester***, which binds to free radicals (byproducts of cytostatics) and neutralizes them, is useful.

The toxic effect of cyclophosphamide and ifosfamide on the urinary bladder can be reduced by the simultaneous administration **of mesna,** a drug that binds specifically to acrolein and neutralizes it. Usually, as many units by weight as cyclophosphamide are applied.

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 transaminases in the serum), but with the use of high doses of cytostatics, damage and obliteration of small branches of v. portae, resulting in portal hypertension. The following cytostatics have the most pronounced hepatotoxic action: mercaptopurine, cyclophosphamide, asparaginase, plicamycin, nitrosoureas, methotrexate, busulfan, hydroxyurea.

Lung damage is primarily caused by the cytostatic bleomycin. It is concentrated in lung tissue, because it has a small amount of hydrolase enzyme, which breaks down bleomycin. Bleomycin has a direct toxic effect on type 1 pneumocytes and pulmonary capillary endothelial cells. As a consequence of the action of bleomycin, lung fibrosis gradually develops.

Damage to the skin and its adnexa is also caused by a number of cytostatics. Fluorouracil, doxorubicin, sunitinib and methotrexate can cause so-called hand-foot syndrome, which manifests as dry, red palms and soles that gradually become hyperpigmented. Busulfan, bleomycin, methotrexate, thiotepa and fluorouracil can also cause hyperpigmentation on other parts of the skin. Taxanes and bleomycin can cause nail loss.

TOXICOLOGY

PROCEDURE WITH THE POISONED

Modern times are 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 increasing, 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 everywhere in the world, including in our country.

In the treatment of a poisoned person, initial therapy is of enormous (and often crucial) importance, which must often be undertaken at the place of poisoning or in the first healthcare facility. The first step after encountering a poisoned person is not to make an accurate diagnosis, that is identification of the type of poison. It is usually not even possible, and it would take precious time. Immediately after dealing with the poisoned person, the doctor should take general, non-specific measures that apply to any poisoning. First, it is necessary to ensure the patency of the airways, and then to ensure breathing and heartbeat (heart massage, artificial respiration). A venous line should then be secured and a urinary catheter inserted to monitor diuresis. All the mentioned procedures should not last more than 30 minutes. Of course, if the patient is poisoned by gas or steam, the treatment begins only after the poisoned person is taken out of the room where he was.

Once the basic physiological functions are ensured, the next priority is to prevent the absorption of the poison. If the poison is spilled on the skin and clothes, then the clothes should be removed immediately and the skin should be washed with soap and water. If the poison is swallowed (which is the most common case), you should either induce vomiting or wash out the stomach. Both procedures have the most effect if they are undertaken within one hour of poisoning, and they should be carried out up to 4 hours after poisoning (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, oil and its derivatives or poisons that cause convulsions. The easiest way to induce vomiting is with syrup of ipecac (see the chapter on emetics).

Gastric lavage is performed by introducing a nasogastric probe as wide as possible into the stomach, and then alternately introducing and eliminating warm water through the probe. The procedure is repeated until the water returning from the stomach becomes completely clear. If the patient is unconscious, gastric lavage can only be performed after the airways have been previously protected by inserting an endotracheal tube with coffee. Gastric lavage is contraindicated in patients poisoned with caustic agents or petroleum, as perforation of the esophagus or stomach with the probe may occur.

After removing the poison from the stomach, the patient should be given activated charcoal (1 g / kg of body weight) mixed in water to swallow or, if a probe is placed, a charcoal suspension is poured through it. Activated charcoal is actually activated charcoal obtained by anaerobic combustion of animal remains (bones, ligaments, joint capsules) through a special process. During the activation process, coal particles significantly increase their surface area so that they look like a sponge. Molecules of poison are absorbed on 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 $MgSO_4$ - bitter salt) are mostly 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 aforementioned measures have been taken, the doctor can devote more time to trying to find out what poison the patient was poisoned with. First of all, the statements of the witnesses of the poisoning or the closest relatives should be taken into account; an insight into the place of poisoning (medicine box, poison packaging) can often indicate a solution. Physical examination of a 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 smell; cyanides smell like bitter almonds; the smell of rot occurs after heavy metal poisoning.
4. Tachycardia is caused by anticholinergics, tricyclic antidepressants, cocaine, cyanides; bradycardia is caused by cardiotonic glycosides, β-blockers, calcium channel blockers and others.
5. Cyanosis of the central type is caused by SO and substances that convert hemoglobin into methemoglobin (ni-tritium, for example). The pink color of the skin follows cyanide poisoning, which, by blocking tissue respiration, prevents the utilization of O_2 from oxyhemoglobin.
6. Hypotension is caused by opioids, barbiturates, calcium channel blockers, neuroleptics, anti-depressants.
7. Hypertension is caused by cocaine, amphetamine, ryegrass alkaloids, naphazoline and others.

If conditions exist, samples of vomited contents, stool, blood and urine should be sent to the National Center for Poison Control (located at the Toxicology Clinic of the Academy of Medical Sciences in Belgrade). In any case, the aforementioned Center should be consulted by phone regarding further treatment of the poisoned; his phone is open 24 hours a day.

Further treatment of the poisoned depends on the type of poison. In addition to the symptomatic therapy that treats the effects of the poison (for example, we will treat convulsions with sedatives, heart failure with cardiotonics), sometimes we can apply a medicine 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 μ-receptors and blocks the effects of opioids. Benzodiazepine poisoning can also be treated with an antidote - the benzodiazepine receptor blocker fluma-zenil.

Chelates are a special type of antidote. They got their name from the Greek word keli (κε λλι= cell), because with their nucleophilic radicals (groups with S, N or O) they capture and "close" 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 that came into use was **dimercaprol** (dimercaptopropanol). Dimerca-prole was first used to treat poisoning by the battle poison Lewisite, which contained arsenic. Later, it proved to be very useful for the treatment of *acute* arsenic, mercury and lead poisoning. It has a lot of side effects because it can bind to many cellular enzymes and thus inactivate them (vomiting, salivation, paresthesias, especially thrombocytopenia and reduction of blood coagulability). Hypertension with tachycardia, which dimercaprol can cause after sudden administration, is a special problem. Less toxic than dimercaprol is the thio-derivative of succinate: **succimer**. Succimer is indicated only for the treatment of children whose blood has a lead concentration greater than 450 micrograms/ L ; it is administered orally and effectively reduces the level of lead in the blood, but it remains unclear whether it can improve the damage to the tissues that has already occurred. Adverse effects are limited to gastrointestinal disorders and an increase in transaminase levels (in about 8% of patients).

Calcium - disodium - ethylenediamine - tetraacetic acid acid ($CaNa_2$-E D TA) is a chelate with a special affinity for lead. It is used to treat lead poisoning. Since it also binds calcium to a certain extent, it can sometimes cause hypocalcemia and tetanic spasms. In large doses, it is nephrotoxic.

The chelate deferoxamine is used to treat iron poisoning, and the chelate **penicillamine is used for copper poisoning (or to overload the body with copper in Wilson's disease due to difficult excretion through the bile)**. In addition to iron, deferoxamine also binds aluminum (eg, when aluminum accumulates in chronic kidney failure). M. or i. c. are also applied. It releases histamine (redness of the face, hypotension), turns urine dark red and has a neurotoxic effect. Penicillamine is also highly toxic; as well as dimercaprol, it damages the bone marrow and kidneys. As patients with Wilson's disease must receive this drug throughout their lives, periodic blood and urine control is necessary. The new chelate, **trientine**, which has a high affinity for copper and is significantly less toxic than penicillamine, is used only in patients who cannot tolerate penicillamine.

Antidotes for poisoning with organophosphorus insecticides and war poisons are **atropine** (blocks the muscarinic effects of the poison) and **oximes** (pralidoxime, obidoxime). Oximes regenerate acetylcholinesterases that have been phosphorylated by poisons and thereby inactivated. The effect of oximes is better the earlier they are applied from the moment when the poisoning occurred.

Cyanide poisoning (or an overdose of the antihypertensive sodium nitroprusside) is treated with several antidotes. **Hydroxy-cobalamin** (vitamin B_{12}) directly binds the cyano group and thus prevents its binding to tissues. Application of **Na-nitrite** converts hemoglobin into methemoglobin, which has a high affinity for the cyano group - binds it and thus inactivates it. Finally, the poisoned should receive sodium 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 can be helped if the elimination of the poison from the body is accelerated. This can be done in several ways:

a) **forced diuresis** - reduction of electrolyte and water reabsorption in distal tubules or Henle's loop leads to reduction of reabsorption and poisons from primary urine. The result is an increase in the amount of urine and an increase in the amount of eliminated poison. This effect is achieved by the use of powerful loop diuretics, especially furosemide, with copious saline infusion to maintain blood flow through the kidneys. An additional increase in the excretion of poison can be achieved by using a base ($NaHCO_3$) or an acid (NH_4Cl). By applying a base, the urine becomes alkaline, so that poisons that are weak acids in the tubules of the kidneys are completely dissociated, i.e. semi-rice; as such, they pass the membrane of tubular cells poorly, remain in the lumen and are excreted more 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 using ammonium chloride. In acidic urine, the poison is more dissociated, which means that it is less reabsorbed and more excreted in urine. It is **forced acid diuresis** .

b) **hemodialysis** - with hemodialysis, poisons of lower molecular weight can be removed, which in the body bind little to plasma and tissue proteins, whose volume of distribution is not too large, so 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 the case of poisoning with antidepressants and neuroleptics.

c) **hemoperfusion** - is the procedure of passing the patient's blood through tubes lined with activated charcoal. Poisons that have large, polar molecules are absorbed on the particles of this coal. Hemoperfusion is the method of choice for detoxification of methylxanthines (theophylline, caffeine), barbiturates (phenobarbitone), phenytoin, carbamazepine and salicylates. The condition for successful removal of poison by hemoperfusion is that it is a substance whose volume of distribution is not too large, so that its concentration in the blood is relatively high.

MANIFESTATION OF TOXIC EFFECT

Poisons, as well as drugs in supramaximal doses, bind to the macromolecules of the cells of the human body, and disrupt their functioning. If macromolecules vital to the cell are blocked, cell death will occur, either suddenly (necrosis) or gradually, by 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 a lot on whether the poison is metabolized in it or not. If the poison itself is not very biologically active, but is transformed into toxic metabolites under the action of cytochrome P 450, then the liver cells *around the central vein of the lobule* will suffer the most (because cytochrome P 450 activity is highest in those cells). If the poison is active by itself, the cells *around the portal areas will suffer the most*, because they are exposed to the highest concentration of the poison. If the liver damage is not a direct result of the poison, but an allergic reaction to the poison or drug, areas of dead cells will be scattered throughout the liver.

When the poison affects the kidney, the cells of the proximal tubules suffer the most being exposed to the highest concentration of poison. 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 infection. All cytostatics and immunosuppressants have such an unwanted effect, so when using them, the number of leukocytes in the patient's blood must be constantly controlled.

In the central nervous system, toxic manifestations are primarily caused by poisons that are liposoluble, so they easily pass through the hemato-encephalic barrier (eg organic solvents, insecticides). The central nervous system reacts to poisons first with disorders of consciousness (confusion, drowsiness, disorientation) and perception (illusions and hallucinations), and then with the appearance of convulsions.

GAS POISONING

Carbon monoxide (SO). It is created during combustion in conditions without enough oxygen (closed rooms, garages). The affinity for iron in hemoglobin is 200 times higher than the 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 soporific and finally comatose state. Since the blood does not carry enough oxygen, cyanosis of the central type occurs. The patient dies due to cardiac arrest and respiratory failure. The treatment consists of taking the patient out of the room with SO and then applying 100% oxygen through a mask. If there is a hyperbaric chamber, the patient can recover faster if exposed to pure oxygen at a pressure of two atmospheres. O_2 removes SO from binding with hemoglobin.

Sulfur dioxide (SO_2). Sulfur dioxide is an industrial gas produced during the burning of fossil fuels, so poisoning is the most common among production workers. SO_2 dissolves in the mucous membrane of the bronchi and forms sulfuric and sulfuric acids with water 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 (NO_2) and ozone (O_3) are gases that cause a number of industrial poisonings. Nitrogen dioxide poisoning most often occurs in workers who work with silage on agricultural goods or in people who work near internal combustion engines. Unlike SO_2 which damages the upper respiratory tract, NO_2 and O_3 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

Lead poisoning. Lead most often enters the human body through the gastrointestinal tract, in the form of inorganic and organic compounds. Poisoning of small children who put lead-based paints in their mouths was particularly common.

Lead can cause acute poisoning if ingested in large quantities at once. Acute poisoning can also occur during prolonged inhalation of gasoline vapors containing an 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 onset of anemia, occasional colic-type 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, the most common being irritability , tremor, memory disorders and peripheral neuropathy) and, less often, interstitial nephritis.

Lead poisoning is treated with the use of chelate, but only if the patient has symptoms of poisoning; preventive application of chelate is contraindicated. $Ca\text{-}Na_2\text{-}EDTA$ (1 g i. v./12 hours during 3-5 days for adults, and 50 mg / kg /day i. c. in children) or dimercaprol (300-450 mg / m^2 /day i. m.). 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, the folk remedy against ileus was mercury; the patient would drink about a hundred grams of mercury, which could sometimes establish a passage through the digestive tract with its weight). 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 fish species. In Japan, there have been several cases of mercury poisoning due to ingestion of the flesh of such fish.

Acute mercury poisoning is primarily manifested by irritation of the gastrointestinal tract (vomiting, nausea, diarrhea), which soon leads to damage to the renal tubules.

Chronic poisoning is characterized by tubular kidney damage, damage to the basal ganglia of the cerebrum (disordered handwriting, irritability, personality disorders, ataxia, chorea, athetosis, tremors) and mercury rim on the gums. 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 by suction. 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, inactivates them and leads to impaired function or death. Both elemental arsenic and its compounds (both inorganic and organic) are poisonous. Large amounts of arsenic are released when coal is burned and when ore is smelted. Also, arsenic has been used by criminals for centuries to poison people and animals. Arsenic is most toxic when it is trivalent (eg in arsine gas: A sH_3).

Arsenic has a toxic effect on the nervous system, bone marrow, liver, respiratory tract, skin and kidneys.

Inorganic arsenic compounds ingested in larger quantities lead to acute poisoning: severe gastroenteritis, laryngo-tracheo-bronchitis and shock occur. If an acute attack is survived, bone marrow depression, encephalopathy, and peripheral sensory neuropathy occur. The patient smells like garlic.

Organic arsenic compounds only cause encephalopathy when ingested acutely.

A special form of acute arsenic poisoning is poisoning with arsenic gas (A sH_3). Acute hemolysis dominates here because arsine binds to hemoglobin and oxidizes, turning into a hemolytic agent. Due to sudden hemolysis, a large amount of hemoglobin is found in the plasma, 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, hair falls out and nails acquire whitish lines (Mi's lines). Depression of the bone marrow results in anemia and pallor, which is partially dotted with pale-to-red spots (due to vasodilation): the so-called tan milk and roses. The patient is cachectic, suffering from sensory neuropathy, conjunctivitis and loss of renal function.

Arsenic poisoning is treated with dimercaprol (3-5 mg / kg i. m . for 4 hours during the first 48 hours, then every 12 hours for 10 days).

Beryllium poisoning. Beryllium is used in alloys to make electrical equipment. In the body, it mostly binds to enzymes that use magnesium as a cofactor, and inhibits them. If inhaled, beryllium causes *acute pneumo-nitis* followed by pulmonary edema. Symptoms usually appear after a latent period of several days. Long-term inhalation of small amounts of beryllium results in chronic poisoning, which is characterized by the appearance of *granulomas* in the lungs. Over time, respiratory insufficiency develops, and patients are at a higher risk of developing lung cancer.

If beryllium comes into contact with the skin, acute dermatitis develops, with redness and blistering.

In case of acute beryllium poisoning, Ca-Na_2-E D TA, corticosteroids and antibiotics should be used.

HYDROCARBON 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 aspirated than if swallowed. For example, if he swallows 1 liter of gasoline, the patient will do better than if he aspirated 1 milliliter! During aspiration, these substances cause severe bronchopneumonia and pulmonary edema. That is why it is of the greatest importance when treating patients who have swallowed petroleum distillates not to lead to 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 action of catecholamines, which creates the conditions for the occurrence of arrhythmias. In case of 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 the most used as solvents in rubber and plastic adhesives. The lethal dose of these substances is 2-5 g / kg of body weight, if they are ingested by inhalation or parenterally. After acute poisoning by inhalation or ingestion, they penetrate into the central nervous system, and the appearance of first euphoria, then nausea, blurred vision, tremors, loss of consciousness and convulsions. Arrhythmias can occur due to sensitization of the myocardium to catecholamines. The 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 vapor glue due to euphoria), 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, trichlorethylene, 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 intake or inhalation. Because they are liposoluble, they penetrate the central nervous system causing confusion, loss of consciousness and convulsions. It is characteristic that they damage the liver and kidneys, often after a latent period of several days. They cause centrolobular necrosis in the liver, because they are transformed under the action of cytochrome P 450 to even more toxic metabolites. They also sensitize the myocardium to catecholamines, thereby increasing the tendency for arrhythmias to occur.

Chronic ingestion of these substances leads to encephalopathy, with the following symptoms: memory loss, fatigue, tremors, blurred vision and loss of peripheral color vision.

When halogenated hydrocarbons are burned in a closed space (eg in a fire), they decompose into **phosgene** ($CoCl_2$), a very toxic gas that causes acute pulmonary edema.

There is no specific treatment.

INSECTICIDE POISONING

According to their chemical composition, insecticides are divided into three large groups: organic chlorine compounds, cholinesterase inhibitors and insecticides of plant origin.

a) Poisoning by organochlorine insecticides (dichlordi-phenyl trichloroethane- DD T, lindane, aldrin and others) is characterized by stimulation of the CNS. These substances prevent the inactivation of Na^+ channels in the neuron membrane and lead to tremors and convulsions. Also, they 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 by herbal insecticides. Plant insecticides (rotenone, pyrethrins, nicotine) are sufficiently liposoluble to penetrate the CNS. They cause stimulation of the CNS, which is manifested by tremors, hallucinations and convulsions. There is no specific antidote, but poisoning is treated symptomatically with anticonvulsants and sedatives. In addition to the effect on the CNS, rotenone irritates the mucous membrane of the digestive and respiratory tract, and nicotine leads to hypertension, arrhythmia and neuromuscular blockade of the depolarization type (nicotine activates receptors on the neuromuscular plate and leads to membrane depolarization; Ca^{++} - channels open , Ca^{++} enters the cells and contraction occurs. Ca^{++} channels then spontaneously inactivate, Ca^{++} entry decreases and 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 quickly metabolized, 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 followed by extreme muscle hypotonia. Blood pressure drops, and stays at low values for a long time. Liver and kidney damage manifests in those who survive the coma phase.

Long-term exposure to these compounds increases the risk of Hodgkin's lymphoma or soft tissue sarcoma.

Along with chlorophenoxy compounds, tetrachlorodibenzo-p-dioxin (TCDD, dioxin) is often found as a decomposition product or an impurity created during the production process.

Dioxin causes acne on the skin, muscle pains that intensify during physical activity, insomnia, emotional lability, irritability and loss of libido for several days after entering the human body. Experiments on animals have shown its strong mutagenic effect.

Of **the bipyridyls**, paraquat is the most widely used herbicide. It inhibits the superoxide-dismutase enzyme in the lungs, due to which the lung parenchyma becomes particularly sensitive to the toxic effects of oxygen. It is also converted to a reduced monocationic form, which is then reoxidized, and in the presence of oxygen forms superoxide anion which damages pneumocytes. After oral intake, irritation of the digestive tract (bleeding, pain) immediately occurs. The condition may begin to improve, but after a few days pulmonary edema may occur, progressing to pulmonary fibrosis. Myocardium and liver damage also occur. Paraquat is an extremely toxic substance, because the lethal dose for humans after oral intake is only 4 mg / kg .

Poisoning therapy is only symptomatic.

RODENTICIDE POISONING

Fluoroacetate is metabolized into fluorotricarbonic acid, which inhibits the Krebs cycle. It has a toxic effect on all tissues. In acute poisoning, there are signs of CNS stimulation (vomiting, excitability, convulsions) followed by coma with respiratory depression. In addition, pulmonary edema occurs. Poisoning is treated with glyceryl monoacetate (0.5 ml / kg and . v .) or ethyl alcohol (0.5 ml / kg 10% solution). Due to its extreme toxicity (lethal dose is 50-100 mg), fluoroacetate is no longer used as a rodenticide.

Thallium was widely used as a poison for rats and ants. There is usually a latent period of several days between the ingestion of the poison and the appearance of the first symptoms. There are signs of damage to the peripheral (ptosis, paresthesias, *pain in the extremities*) and central (tremor, confused speech, choreiform movements, convulsions) nervous system. *Hair falls*, the skin atrophies, and a blue border 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 ***sea onion*** (Scila maritima) plant, which are rich in cardio-tonic 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 the appearance of bleeding, and the patient can be helped by the administration of vitamin K.

CYANIDE POISONING

Compounds containing the cyano group (CN) are released in larger quantities during industrial metal processing; the cores of hard fruits (eg 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, coming 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 given intravenously, as a 25% solution, at a rate of 2.5-5 ml . 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 cyanides into thiocyanates, which are non-toxic.

Finally, the patient should be given **hydroxycobalamin**, which binds cyanide and turns into non-toxic cyanocobalamin. The dose is 50 mg / kg .

ETHYL ALCOHOL

Ethyl alcohol (ethanol) is found in various beverages that are obtained by boiling and then distilling materials of plant origin 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 100 ml of beverage. So beer has 3-4 % , wine about 10 % , and "strong" drinks about 40 % of pure ethanol. Ethyl-alcohol first leads to excitation (due to the elimination of cortical control, the alcohol user loses moral norms of behavior) and then CNS inhibition (drowsiness, motor incoordination, in larger doses, sleep and coma). It also causes hypoglycemia and hypothermia. The mechanism of action of alcohol has not yet been determined with certainty. The fatal dose for an adult is 400 ml of pure ethanol, so about 1 L of "strong" drink.

Alcohol is metabolized in the liver under the action of alcohol dehydrogenase. First it turns into acetaldehyde and then into acetic acid. Disulfiram prevents the transformation of acet-aldehyde into acetic acid and thus leads to the accumulation of acet-aldehyde. Acetaldehyde is toxic and causes nausea, vomiting and redness of the upper body. Disulfiram is sometimes given to patients being treated for alcoholism to prevent them from taking alcohol again; if the patient takes a glass of alcohol while on disulfiram therapy, he will experience the already mentioned unwanted effects. There is also a substance that inhibits the formation of acetylaldehyde from ethanol: 4-methylpyrazole (fomepizole). The capacity of the liver to metabolise alcohol is very limited and it becomes completely saturated already after consuming a small amount of alcohol. Regardless of the amount ingested, the same amount of alcohol is 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 7-10 g of pure alcohol in one hour.

Alcohol poisoning is primarily treated symptomatically. The vital functions of the poisoned person should be maintained (artificial or assisted breathing, fluid infusions to maintain kidney function, general care) until the liver eliminates the alcohol and the depressant effect on the CNS is removed. Application of 5% glucose is preferable, because hypoglycemia often develops in poisoned patients; along with glucose, vitamin B1 (thiamine), 100 mg intramuscularly, must be given in order to avoid the formation of lactic acid. In the most severe poisoning, ethyl alcohol can be successfully eliminated by hemodialysis.

The concentration of alcohol in the blood can be measured to assess the degree of intoxication. A concentration below 150 mg / dl means moderate, between 150 and 300 mg / dl medium and above 300 mg / dl severe poisoning. A concentration of 400 mg / dl or more is often lethal.

METHYL ALCOHOL (METHANOL) POISONING

Methanol (CH_3OH) is found in larger quantities in low-quality alcoholic beverages. In industry, it is used as an organic solvent or propellant. Methanol, like ethyl alcohol, leads to depression of the CNS. However, the metabolism of methanol (in the liver, under the action of alcohol dehydrogenase) produces first formaldehyde, and then extremely toxic formic acid (HC OO H). Formic acid causes acidosis and is neurotoxic: blindness, convulsions and severe headache occur. Blindness is preceded by a vision disorder that patients describe as experiencing a "snowstorm". It is believed that formaldehyde is responsible for the specific toxic effect on the retina.

Methanol is metabolized and excreted five times more slowly than ethanol. The lethal dose of methanol after oral administration is 60-250 ml .

Methanol poisoning is treated with **ethanol** . Ethanol occupies the alcohol dehydrogenase and prevents the metabolism of methanol to formic acid. 50% ethanol is administered orally, in a dose of 1.5 ml / kg at the beginning, then 0.5-1 ml / kg every two hours, for 4 days. The level of ethanol in the blood should be 100 - 150 mg / dl.

Instead of 4-metilpirazole, fomepizole can be used. It inhibits alcohol dehydrogenase and prevents the conversion of methanol into formaldehyde. The initial dose of fomepizole is 15 mg / kg intravenously, in a slow infusion; the same or slightly smaller dose can be repeated every 12 hours. The drug can cause headache and hypotension.

In the case of the most severe poisoning, hemodialysis should be used, which successfully removes methanol and formic acid. The presence of acidosis is treated with intravenous sodium bicarbonate.

ETHYLENE GLYCOL POISONING

Ethylene glycol is used as an organic solvent and as an antifreeze. After oral intake, it causes irritation of the gastro-intestinal tract and depression of the CNS (similar to ethyl alcohol). As it is metabolized in the liver under the action of alcohol dehydrogenase (turns into oxalic acid), CNS depression improves after some time and the patient enters the so-called **latent phase**. Meanwhile, oxalate accumulates in the body, binds C a $^{++}$ from the serum and provokes symptoms of tetany due to hypocalcemia. In addition to oxalates, esters and ethers of ethylene glycol are formed, which also have a toxic effect on the brain and other organs. Hypoglycemia also occurs. **The third stage** of poisoning is damage to the kidney tubules due to the deposition of calcium oxalate, which can end in acute kidney failure.

The lethal dose of ethylene glycol is about 100 g.

Treatment of ethylene glycol poisoning includes the use 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 (10 ml of 10% solution), and hypoglycemia by infusion of 5% glucose.

MUSHROOM POISONING

About 2,500 types of mushrooms grow in Europe, of which 30 types are poisonous in our country, and 7 of them cause fatal poisoning. Mushroom poisoning is called **mycetism** (from the Greek word *myces* , which means fungus). The most practical division of mushroom poisoning is into those with a short latency and those with a 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 a short latency ; depending on the mechanism of action of the toxins, 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 lead mine (Entoloma lividum), spittlebug (Russulla emetica), madder (Boletus satanas), stink bug (Russulla foetens) and others. In the treatment, rehydration with solutions for intravenous administration is used.
b) antabuse syndrome, which consists of symptoms similar to those when taking alcohol and disulfiram at the same time (redness of the neck and face, tachycardia, headache, feeling of suffocation); it is caused by the mushroom (Coprinus comatus), if an alcoholic drink is consumed along with it.
c) Pantherina syndrome, which resembles atropine poisoning; it is caused by panther mushroom (Amanita pantherina). This poisoning is treated only with general measures.
d) muscarinic syndrome, which occurs due to the action of toxine muscarine, which binds to muscarinic receptors and activates them; the poisoned person feels heat in the skin (due to vasodilatation), his vision is blurred (due to spasm of accommodation and miosis), bradycardia occurs (due to direct action

on muscarinic receptors on the heart) and hypersalivation. This syndrome is caused by mushrooms from the genera Inocybe and Clitocybe, but also by flies (Amanita muscaria, bright red mushroom hat with white spots); flies are about 100 times less poisonous than Inocyba and Clitocyba. Muscarinic syndrome can be successfully treated with atropine.

Mushroom poisoning with long latency

a) In our country, the most important causes of this type of poisoning are boletus mushrooms (green boletus - Amanita phalloides, white boletus - Amanita verna). These mushrooms have cyclic polypeptides amanitin and phalloidin, which are resistant to the action of digestive enzymes, are absorbed and cause the death of liver cells and submucosal bleeding in the gastrointestinal tract. Amanitin is far more toxic, because 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 appears, which spontaneously resolves in 2 days. Then the patient's condition temporarily improves, only to suddenly deteriorate after 7-10 days, with hepatitis followed by jaundice. In case of severe poisoning, this sequence of events can be faster, and hepatitis is accompanied by kidney and heart failure. The 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 the treatment is reduced to the application of general measures. Poisoned people are given very large doses of penicillin G intravenously (1,000,000 I J per kilogram of body weight), because it partially prevents the poison from entering the hepatocytes and binding to the 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 by mouth 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 budworm poisoning is controversial. Silymarin is an extract obtained from the plant Silybum marianum (vernacular name: adder's grass), and contains about 50% silybin, while the rest consists of silyristin 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 for the treatment of Amanita phalloides poisoning, but also for the treatment of 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 occurs especially often in people who eat the mentioned mushroom, and are otherwise on chronic therapy with statins. The mechanism of the toxic effect is not yet clear. A poisoned person feels nauseous (not vomiting), muscle weakness and sweating. Creatine kinase is highly elevated in the serum, as well as the liver enzymes alanine and aspartate aminotransferase. Then severe myocarditis develops, leading to acute heart failure. Due to rhabdomyolysis, a large amount of myoglobin is released into the blood, which can block the renal tubules and cause acute renal failure. Mortality is around 20%. There is no specific antidote for this poisoning.

c) A syndrome similar to paraquat poisoning occurs if Cortinarius mushrooms are eaten. They contain the substance orelanin, similar in chemical structure to paraquat, 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 mushroom ingestion (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 go from acute to chronic kidney 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 of America. These mushrooms are mostly poisoned by people who are looking for the so-called Matsutake edible mushrooms, which look a lot like Amanita smithiana. These mushrooms produce the toxin allenic norleucine (amino-hexadienoic acid) which acts selectively on the cells of the renal tubules and leads to their necrosis. A few hours after the ingestion of mushrooms, mild gastrointestinal complaints are experienced, which soon pass, but 3 to 6 days later, acute

renal insufficiency occurs. On kidney biopsies a few weeks after poisoning, signs of interstitial fibrosis and tubular necrosis can be seen. Patients are kept alive by hemodialysis, so that after a month or two, kidney function generally improves to the point where dialysis is no longer needed.

SNAKE BITE

The bite of a poisonous snake causes poisoning with snake venom, 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: **viper** (Vipera ammodytes) and **hinge** (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. He is not timid, he likes rocky terrain. The hinge is about 75 cm long , it has a wider and rounder head than the viper. She has a white stripe along the edge of her upper jaw, her eye is large, with a red glow, and there are three large horn plates on her crown.

In snakes, the poison is found in modified salivary glands behind the eye, which are connected to two hollow teeth at the top of the upper jaw (length about 5-7 mm) by an excretory canal. When a snake bites a human, the venom from the glands is injected through those two teeth into the subcutaneous tissue. The venom contains enzymes protease, phospho-lipase, oxidase, hyaluronidase, as well as factors that affect the blood clotting process.

Pain, swelling, blue color of the skin and subcutaneous bleeding occur at the site of the bite. Hypotension occurs, sometimes a shock state. Due to blood coagulation disorders, bleeding occurs from the gums, uterus, testicles, colon or stomach. If shock develops, anuria and acute renal failure may occur. The severity of the clinical picture depends on the amount of poison that was injected, and on the body weight of the person who was bitten. The most vulnerable are children under 5 years old.

A person who has been bitten should be made to rest immediately, and the extremity where the bite is located should be immobilized with a splint. Wash the wounds from the snake's teeth with water, and connect them with a 5 mm deep incision . Then suck out the poison with your mouth or with a rubber pump (up to 30% of the poison can be removed this way). Place bandages with a rubber hose or tape above and below the bite, and tighten them so much that they obstruct the lymph flow, not the arterial and venous blood flow. Move the curtains every 20 minutes, as the swelling spreads. Transport the patient to the hospital as soon as possible.

As soon as possible (at the latest within 4 hours), the patient should receive serum against snakebite, which is obtained by immunizing the horse with snake venom. Before applying the serum, it should be checked whether the patient is allergic to it. This is done by intradermal injection of 0.02 ml of diluted serum with physiological solution in the ratio of 1:100, and observation for 10 minutes. Normal physiological solution should also be injected intradermally, as a control. If there is no swelling with redness, the patient can then be given the serum.

The serum is given in an intravenous infusion, diluted with physiological solution. At least 3 ampoules of serum of 3000 IJ each should be given . In addition to antiviper serum, the patient should be given antibiotics and antitetanus serum. It is also necessary to correct coagulation disorders and fight against circulatory shock.

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. Then, before applying the serum, we carry out the desensitization procedure. The serum is diluted with physiological solution in a ratio of 1:100, and 0.05 ml is injected subcutaneously . Then, double the amount is injected every 5 minutes , until 1 ml of serum diluted in a ratio of 1:10 is consumed . If there is no reaction then, dilute the entire amount of serum in a ratio of 1:50, and apply it by slow intravenous infusion, drop by drop. Have with you all the necessary medicines to fight against anaphylactic reaction: adrenaline, corticosteroids, antihistamine.

ACID AND BASE POISONING

If strong acids or bases are swallowed, they cause the death (necrosis) of all structures with which they come into contact. First of all, necrosis occurs on and around the lips, in the oral cavity and on the esophagus. Acids lead to so-called ***coagulation*** necrosis, which is rigid and retains the shape of the organ that has been damaged. Bases lead to ***colliquative*** necrosis, in which the affected tissue turns into a mushy mass. With acid and base poisoning, the patient suffers severe pain, and is usually in a state of cardio-vascular collapse. Under no circumstances should such patients be induced to vomit, nor should their stomach be washed! Both interventions will end with perforation of the esophagus, which directly results in fatal mediastinitis. At first, the patient should only be given to drink water or milk (a couple of liters) in order to dilute the ingested acid or base (but only if the poisoned person was found immediately after ingestion of the poison). Opioid analgesic morphine should also be given to control pain. The poisoned person should then necessarily be hospitalized, and the cardiovascular collapse should be suppressed with infusions, and the infection with antibiotics.

The patient must not take any food for several weeks, until the wounds in the oral cavity and esophagus heal. Then will begin a long-term and persistent struggle with esophageal strictures due to fibrosis, which are treated with the use of corticosteroids and bouging (dilation of the esophagus using metal rods). In the meantime, the patient is fed parenterally.

Bases usually cause deeper necrosis than acids, but with acid poisoning, an additional complication may occur in a small number of patients: acute renal failure. During the coagulation of the esophageal tissue, abnormal proteins of smaller molecular weight are sometimes formed, which penetrate the blood, reach the kidneys, and there, after filtration in the glomeruli, 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 applying high doses of Henle's loop diuretics and intensifying infusions of crystalloid solutions.