PHARMACOLOGY

AND

TOXICOLOGY ESSENTIALS

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THE CONTENT

GENERAL PHARMACOLOGY

We use the name substance for any chemical entity, from elements to the most complex compounds. Substances that have biological activity, i.e., exert some effect in the human organism, they can be classified as drugs and poisons in the narrower sense. Medicines are biologically active substances that can be used to diagnose, prevent or treat diseases, while poisons in the narrower sense are substances that have exclusively harmful

effects in the human body. The drug can also become a poison, if it is administered in excessive doses, i.e. overdose.

The part of pharmacology that deals with the effect of drugs on the human body is called pharmacodynamics. The drug can act on the human body specifically, by binding to a specific place in the body, which we call a receptor (usually these are molecules of functional proteins). In that case, the effect of the drug will be limited only to the structures of the organism that have the appropriate receptor on them, thus achieving a precisely determined effect with a minimum of side effects on other structures. Most of the drugs we use today act specifically, which reflects the intensive development of pharmacology in the past. Nevertheless, today we still use a certain number of drugs whose mechanism of action is non-specific, i.e. it manifests itself on all cells and tissues that the drug encounters. For example, we still use hypertonic sodium chloride solution today, and very successfully, for the treatment of chronic sinusitis, because such a solution "draws" water from the mucous membrane of the nasal passages by the forces of osmosis, thus reducing swelling of the mucous membrane and opening the entrances to the sinuses, enabling the drainage of purulent contents and healing.

The drug binds to the receptor either by weak bonds or by strong covalent bonds. If it binds with weak bonds, then it can be displaced from the receptor by another drug (or some endogenous substance) that binds to the same receptor. This type of antagonism between two drugs is called COMPETITIVE ANTAGONISM. If the drug binds to the receptor with strong covalent bonds, then that receptor is permanently inactivated, i.e. it completely loses its function. The effect of such a drug will stop only after the cells synthesize a new receptor, which usually happens within 24 hours. We call this type of antagonism NON-COMPETITIVE ANTAGONISM.

When agonists bind to the receptor, they cause certain changes in the cell, which result in a certain effect. We call these changes INTERNAL ACTIVITY. When the antagonist binds to the receptor, it does not cause changes inside the cell, i.e. has no internal activity. The effect of an antagonist can only be exerted if the receptor to which it binds is otherwise under constant activation by endogenous agonists, usually neurotransmitters, hormones or autacoids (local signaling substances).

In order for the drug to exert its effect in the body, it is necessary to activate (or block, if it is an antagonist) a sufficient number of receptors, which means that the patient should be given a sufficient amount of the drug, i.e. dose. The dose of the drug that exhibits the minimum effect, i.e. that activates the minimum number of receptors sufficient to produce a clinically significant effect is called the threshold dose. With an increase in the dose of the drug, we have an increase in the effect until the moment when we have activated all the available receptors in the body; then we have achieved the maximum effect, further

increasing the dose will not be able to increase the effect, but the drug will start to act on other receptors due to the high concentration in the tissues, leading to harmful effects (which we call toxic). The greater the range between the threshold dose (which we also call the minimum effective dose) and the smallest dose that causes toxic effects, the safer the drug is for use, so we say that such a drug has a wide therapeutic range. Medicines with a wide therapeutic range are easy to apply in practice: the doses do not have to be determined too precisely, and in the event that some other medicine raises or lowers the concentration of the primary medicine in the blood (this is called drug interaction), there will be no consequences. Another measure of the relative safety of the drug is the therapeutic index, i.e. the ratio of the drug dose that causes a toxic effect in 50% of patients and the drug dose that causes the desired effect in 50% of patients. Whichever of these two measures we use in practice, it is clear that drugs with a narrow therapeutic range, that is, a small therapeutic index, represent a big problem for patients who take them. Sometimes even a slight increase in the dose can lead to toxic effects. Such drugs include antiepileptics, anticoagulant drugs and cardiotonic glycosides; when we administer drugs from these groups, we try to prevent the occurrence of toxic effects with additional measures, and still achieve the desired therapeutic effect (eg, we measure the concentration of antiepileptic drugs in the blood, we monitor the blood clotting test, we monitor the ECG, etc.).

There are only a few ways that drug receptors work, ie. only a few mechanisms by which receptor activation leads to changes within the cell. According to these mechanisms, all receptors (of which there are hundreds) in the human body can be classified into five groups, which we also call "superfamilies" of receptors. The first group consists of ion channel receptors, which are located in the cell membrane and are made up of several subunits between which there is a passage (channel) for ions. These channels are usually closed, and they open when the drug binds to the receptor, after which ions pass through them according to the concentration gradient, outside the cell - inside the cell, or vice versa. The passage of ions (sodium, potassium, calcium or chlorine) leads to a change in the external and internal charge of the cell membrane, which further leads to the opening of other ion channels that are dependent on the membrane charge and greater entry or exit of the same or other ions. Ultimately, these changes lead to an increase or decrease in the concentration of calcium in the cytoplasm, which is the trigger for cell reactions such as contraction or secretion. Since the opening or closing of ion channels is measured in milliseconds, the response of cells to drugs that act on ion channel receptors occurs very quickly, within a few seconds. The ion channel receptor family includes nicotinic receptors for acetylcholine, ionotropic receptors for glutamate and many others.

Receptor transmembrane enzymes are also located in the cell membrane. The drug binds to the receptor on the outside of the membrane, while the cytoplasmic part of the receptor is actually an enzyme (most often tyrosine kinase, but also serine-threonine kinase,

and tyrosine phosphatase), which phosphorylates or dephosphorylates other functional proteins inside the cell on the amino acid tyrosine. Upon binding of the drug to the receptor, two adjacent receptors are connected by disulfide bridges (dimerization) and then their internal parts are phosphorylated or dephosphorylated. A functional protein that is phosphorylated (or dephosphorylated) becomes active and phosphorylates some subsequent functional proteins, until activation of effector structures in the cell (usually contraction or secretion) occurs. Transmembrane enzyme receptors are used by hormones such as insulin and many growth factors, the effect of which does not have to be immediate, but occurs after several tens of minutes or hours.

Transmembrane receptors linked to Janus kinases are very similar to transmembrane enzyme receptors - the only difference is that the cytoplasmic part of the receptor is not an enzyme, but is in close contact with a special enzyme called Janus kinase. Upon binding of the drug to the receptors, dimerization and subsequent activation of Janus kinases occur, which further phosphorylate functional proteins within the cell. Receptors for inflammatory cytokines belong to the superfamily of transmembrane receptors related to Janus kinases.

The G protein-coupled receptor superfamily is particularly large. They are also membrane receptors whose amino acid chain passes through the membrane 7 times, making functional loops in and out of the cell. Upon binding of the drug to such a receptor, its third cytoplasmic loop activates a protein bound to guanosine-triphosphate (hence the name G-protein), which further leads to the creation of secondary messengers in the cytoplasm. G-protein is inactivated after consuming energy from guanosine-triphosphate and guanosine-monophosphate is formed. This group of receptors includes alpha and beta adrenergic receptors, muscarinic receptors, receptors for pituitary hormones (luteinizing and follicle-stimulating hormone) and many others. After the activation of receptors connected to G-proteins, the effect occurs in a few tens of seconds to a few minutes.

Finally, the fifth family of receptors refers to receptors located in the cytoplasm, i.e. on the so-called intracellular receptors. In order for the drug to be able to act on these receptors, it must be sufficiently liposoluble, in order to first pass through the cell membrane. When it is found in the cytoplasm, the drug binds to the receptor, and that complex then goes to the nucleus, where it affects the expression of certain genes, that is, leads to the synthesis of certain functional or structural proteins. All hormones and vitamins with a steroid structure are sufficiently liposoluble, so their receptors are located inside the cell (eg cortisol, aldosterone, testosterone, estrogen, progesterone, vitamin D). In order for the effect of a drug that acts through an intracellular receptor to develop to the full extent, it is necessary to pass almost a whole day, so when using them, you should count on the latent period until the onset of action, i.e. the effect cannot be expected immediately.

The movement of the drug through the human body, from the place of application to the place of elimination, is a complex process, which consists of absorption, distribution, biotransformation and excretion. The part of pharmacology that deals with the study of drug movement through the body is called pharmacokinetics. Medicines can be administered enterally (through the gastrointestinal tract) or parenterally (all other forms of administration). Enteral administration of the drug, in which the patient swallows the drug, is called oral administration, and it is the route of administration that is most often used, first of all because of its simplicity, and then because of its greater safety than the others. After oral administration, drugs are mostly absorbed in the first part of the small intestine, which is called the jejunum. The jejunum is the longest part of the small intestine, which has a very large surface (its mucous membrane is very folded in the form of villi, and the epithelial cells themselves on the surface of the villi have a folded luminal membrane, the so-called microvilli). After absorption in the small intestine, drugs enter the venous bloodstream of the intestine, from where they enter the liver via the portal vein, and only after passing through the liver do they reach the systemic circulation. If the liver has a large capacity for drug biotransformation, it may happen that only a small part of the absorbed drug reaches the systemic circulation unchanged. In addition, there are two mechanisms in jejunum epithelial cells that further complicate drug absorption: the glycoprotein P pump, which expels drugs back into the lumen, and cytochrome P-450, which degrades drugs by oxidation. In order for the drug to be administered orally at all, it is necessary that the previously mentioned processes allow a significant part of the ingested drug to reach the systemic circulation unchanged, from where it will be taken to the site of action. The fraction (part) of the administered drug dose that reaches the systemic circulation unchanged is called bioavailability.

After absorption and reaching the systemic circulation, the drug is distributed further throughout the body. How far will the medicine reach, ie. whether it will spread only in the blood plasma and extracellular space or whether it will also penetrate into the cells depends on its liposolubility and binding to certain specific transporters, which normally transport the normal components of the organism through the cell membranes, i.e. nutritional and building materials, hormones, neurotransmitters and various other local regulatory factors. Liposoluble drugs and drugs that bind to specific transporters penetrate into the cells and reach the central nervous system, which is normally separated from the blood by a continuous layer of endothelial cells between which there are no open passages (such as antipsychotics or antidepressants, which must penetrate to the brain structure to act). On the other hand, water-soluble drugs without special transporters are mainly distributed in the extracellular fluid (eg penicillins and cephalosporins). Liposoluble drugs are still significantly bound to blood plasma proteins (weakly acidic drugs for albumins, and weakly alkaline drugs for alpha-globulin); the part of the drug that is bound to blood plasma proteins can be seen as a depot of the drug, because it cannot directly reach the site of action

in the tissues, but is only in dynamic equilibrium with the free drug in the blood plasma. The quantity that tells us how far the drug reaches the body is called the volume of distribution. The volume of distribution is calculated as the ratio of drug dose to blood concentration. It is the volume in which the drug would be distributed if the concentration of the drug in all parts of the body were the same as in the blood.

While water-soluble drugs can be eliminated from the body in a relatively simple way through excretion in the kidneys, this is not the case with liposoluble drugs, because after filtration in the glomeruli of the kidneys, they are completely reabsorbed back into the blood in the tubules and collecting ducts of the nephron. In order to eliminate liposoluble drugs, the human organism through evolution has developed processes of biotransformation of such drugs and their conversion into water-soluble metabolites. The main place of biotransformation is the liver, and that process has two phases: the first phase includes oxidation, reduction and hydrolysis, and the second phase is conjugation, i.e. combining the drug with water-soluble substances. Oxidation of the drug is carried out on cytochrome P-450. Some drugs accelerate the oxidation of drugs on cytochrome P-450 (eg, antiepileptic drugs), and other drugs slow down the oxidation (eg, erythromycin). The first are INDUCTORS and the second are INHIBITORS of drug metabolism. The simultaneous administration of such drugs with other drugs that are also biotransformed on cytochrome can lead to a large decrease or increase in the blood plasma concentration of the latter, which results in a decrease or an increase in the effect. Such a phenomenon is called pharmacokinetic interaction between drugs. The conjugation phase involves the binding of a previously oxidized, reduced or hydrolyzed drug with glucuronic, acetic or sulfuric acid, or with the amino acid glycine. Most of the biotransformed drugs (metabolites) are pharmacologically inactive, but a certain percentage may have the same or even greater activity than the drug from which they were created.

Water-soluble drugs and water-soluble metabolites are excreted in the kidney by glomerular infiltration and tubular secretion. Tubular secretion has two systems: cationic and anionic, which are used by weak base and weak acid drugs. The excretion of drugs in the kidney can be greatly affected by the rN of urine, because the drug can become more or less ionized, i.e. more or less water soluble. If the drug is a weak base, it will be more ionized in acidic urine, so it will be excreted more easily (because it will be less reabsorbed through the tubule wall into the bloodstream); if the urine is alkaline, the weak base drug will be less ionized, so less will be excreted. It is exactly the opposite with drugs that are chemically weak acids: they will be more ionized in alkaline urine (and more excreted), and less ionized in acidic urine (and less excreted, because they will be more reabsorbed into the blood from the renal tubules. Since We can change the rN of urine (for example, if the patient takes sodium bicarbonate, the urine will become alkaline, and if he takes vitamin C, it will become acidic), we can also influence the rate of excretion of certain drugs.

We can evaluate how effective the drug elimination process is by determining parameters such as drug clearance and half-elimination time. Drug clearance is the volume of blood plasma that is released from the drug in a unit of time, and half-elimination time is the time for which the concentration of the drug in the plasma falls to half of the initial value. Most drugs are eliminated by linear kinetics after administration of the recommended doses, that is, the elimination is greater if the concentration of the drug in the blood is higher. Fewer drugs are eliminated by saturation kinetics, which means that there is a limited capacity for elimination. With linear elimination kinetics, the drug does not accumulate in the blood, but after repeated administration, a certain stable concentration of the drug is established, with minor variations at the beginning and end of the dosing interval. When treating a patient, we strive to achieve a stable concentration of the drug in the blood, because only then can we expect a stable and reliable effect. The situation in which a stable concentration of the drug in the blood is achieved is called the equilibrium state, because then the entire dose of the drug is eliminated in the dose interval (that is why there is no further increase in the concentration of the drug in the blood). The equilibrium state occurs after 4-5 dosing intervals, which are equal to the half-elimination time of the drug. In the case of drugs that are eliminated by saturation kinetics, it is not possible to achieve an equilibrium state, but in them the drug continuously accumulates in the body; in order to avoid the appearance of toxic effects, we then resort to controlling the concentration of the drug in the blood and reducing the dose.

The speed of drug elimination can also be affected by liver or kidney function. The elimination of drugs in liver disease is reduced only if a severe form of liver failure has occurred. Then usually the dose should be reduced by 50%. In case of renal insufficiency, if the drug is excreted unchanged through the kidneys by more than 70% (or if the sum of the excreted unchanged drug and its active metabolite is greater than 70% of the total ingested drug) and if the insufficiency is moderate (creatinine clearance 20 - 50 ml/ min) the dose of the drug is reduced by 50%. If there is severe renal insufficiency (creatinine clearance less than 20 ml/min), the dose of the drug is reduced by 50% and the dose interval is doubled.

In elderly people (over 65 years old), the doses of most medicines should be reduced by at least 30%, because muscle mass decreases in old age, the eliminative power of the kidneys decreases and because elderly people are more sensitive to the effects of medicines. Some drugs should not be used at all in the elderly, because they can lead to erosive gastritis with bleeding (e.g. diclofenac), worsening of cognitive ability (orientation, thinking and memory, e.g. after the use of benzodiazepines), worsening of glaucoma or urinary retention (e.g. antihistamines first generation due to anticholinergic effect) and second. That is why the so-called Beers' list of drugs that should not be given to the elderly; the list is available on the Internet, and doctors are expected to respect it, i.e. not to prescribe drugs from the list to the elderly.

The use of medicines in children requires special attention, especially the younger the child. Newborns and infants in the first three months of life have still undeveloped mechanisms of drug elimination. Kidney function is very low, and it progressively increases to normal values only by the end of the first year, and in the first three months, cytochromes and conjugation mechanisms in the liver still do not have full capacity. That is why the doses of medicines for newborns and very small infants per kilogram of body weight are significantly lower than for older infants. Although there are certain formulas for recalculating the dose of medicines for children based on the dose of medicines for adults, in practice they should not be used, because they are imprecise. Medicines for children are dosed exclusively based on the recommendations from the Summary of Characteristics of Medicines, which are usually per kilogram of the child's body weight. Also, in very young children, we avoid the intramuscular route of drug administration, because due to the underdevelopment of the muscles, intramuscular injections would cause great damage, which would manifest itself as contractures later in life.

When it comes to women, the use of drugs outside the period of pregnancy and lactation does not have any significant specifics in relation to the use of drugs in men. However, the use of drugs during pregnancy may carry the risk of congenital anomalies (if the drug is used during the first trimester) or of fetotoxic effects (if used in the second and third trimesters). The occurrence of congenital anomalies due to the use of drugs in the first trimester is called a teratogenic effect. Medicines differ widely in their propensity to cause congenital anomalies or fetotoxic effects. In some cases, the risk is up to 10% (eg, with the antiepileptic drug valproate), and in some cases, it is not at all increased compared to the risk in people who did not take drugs during pregnancy (eg, with the use of penicillin or cephalosporin). For a good assessment of the risk of congenital anomalies after the use of a drug, it is necessary to consult the literature and look for the results of observational studies published in medical journals. Regarding the use of drugs during lactation, it should be remembered that all drugs penetrate into the mother's milk, but the percentage of the dose given to the mother that reaches the child varies greatly from drug to drug. Hence, it is necessary to carry out a risk assessment for each medicine separately, based on the published results of observational studies.

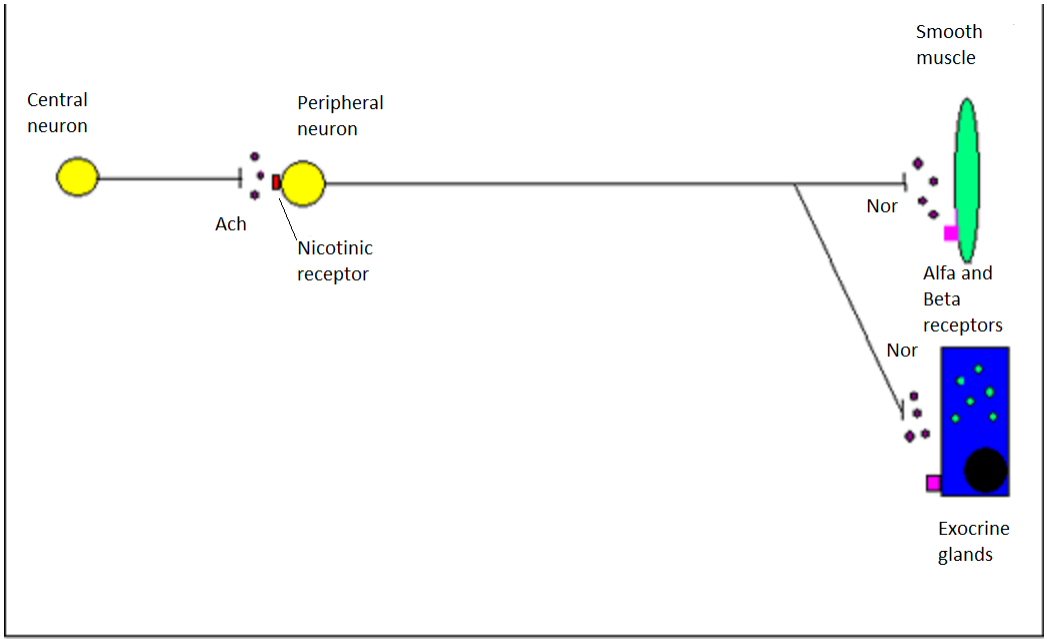
In order for a drug to receive permission to be prescribed to patients in routine practice, it must first be tested in animal experiments and then through clinical studies. Experiments on animals examine the effect of the drug on various organ systems, as well as its toxicity (acute and chronic), and possible adverse effects on fertility and reproduction, potential carcinogenic and mutagenic effects. Only if it is shown in experiments on animals that the drug is not very toxic, testing on humans continues, i.e. clinical studies. Clinical trials of drugs are performed in four phases: (1) testing on healthy volunteers (pharmacokinetics of the drug is investigated); (2) a trial in a small number of patients,

using several different doses, to determine which is the most optimal; (3) testing on a large number of patients, using the principle of a mandatory control group, random assignment of patients to the control or experimental group and double blinding (neither the doctor nor the patient knows whether the patient is receiving a drug or a placebo, i.e. a substance without a pharmacological effect); and (4) epidemiological studies, which are conducted after the release of the drug into the market, and have an observational character.

AUTONOMIC NERVOUS SYSTEM (ANS)

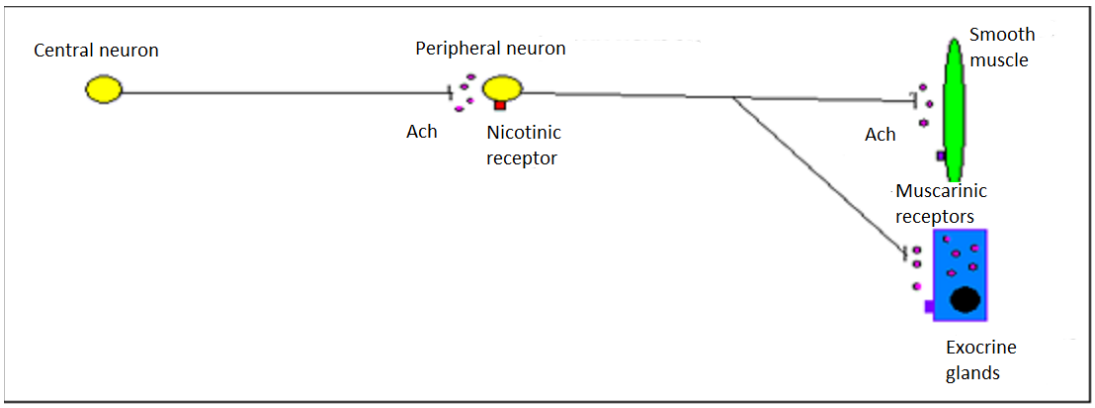
Functionally, the autonomic nervous system (so called because we cannot influence it with consciousness) consists of sympathetic and parasympathetic. Functionally, the sympathetic nervous system has a central and a peripheral neuron. The axon of a central neuron is also called a preganglionic fiber. A peripheral neuron (also called a ganglion cell, because it is located in macroscopically visible clusters of nerve cells called ganglia) sends its axon to effector cells. The axon of a peripheral neuron is also called a postganglionic fiber. At the end of the preganglionic fiber, acetylcholine is secreted and acts on the nicotinic receptors on the ganglion cells. At the ends of postganglionic fibers, noradrenaline is secreted, which acts on alpha and beta receptors on effector cells (mainly smooth muscle cells and glandular cells). Although there are several subtypes of alpha and beta receptors, only alpha1 (α1) and alpha2 (α2) of alpha receptors, and ß1 and ß2 of beta receptors are significant in therapeutic terms. Alpha1 receptors are postsynaptic, and through them the effects of noradrenaline on the smooth muscles of blood vessels and sphincters of the urinary and gastrointestinal tract are transmitted. Alpha 2 receptors are presynaptic, and their function is to limit the release of neurotransmitters from nerve endings. Both beta 1 and beta 2 receptors are postsynaptic: beta 1 are found in the heart and kidney, and beta 2 on the smooth muscles of the respiratory tract and uterus, where they lead to relaxation.

Figure 1. Functional organization of the sympathetic nervous system.



The parasympathicus also has preganglionic and postganglionic fibers. At the ends of preganglionic parasympathetic fibers, acetylcholine is secreted, which acts on nicotinic receptors on ganglion cells. Acetylcholine, which acts on muscarinic receptors, is also secreted at the endings of parasympathetic postganglionic fibers. There are five subtypes of muscarinic receptors, but the most important of them are M2 (located in the heart) and M3 (located on smooth muscle cells and exocrine glands).

Figure 2. Functional organization of the parasympathicus.

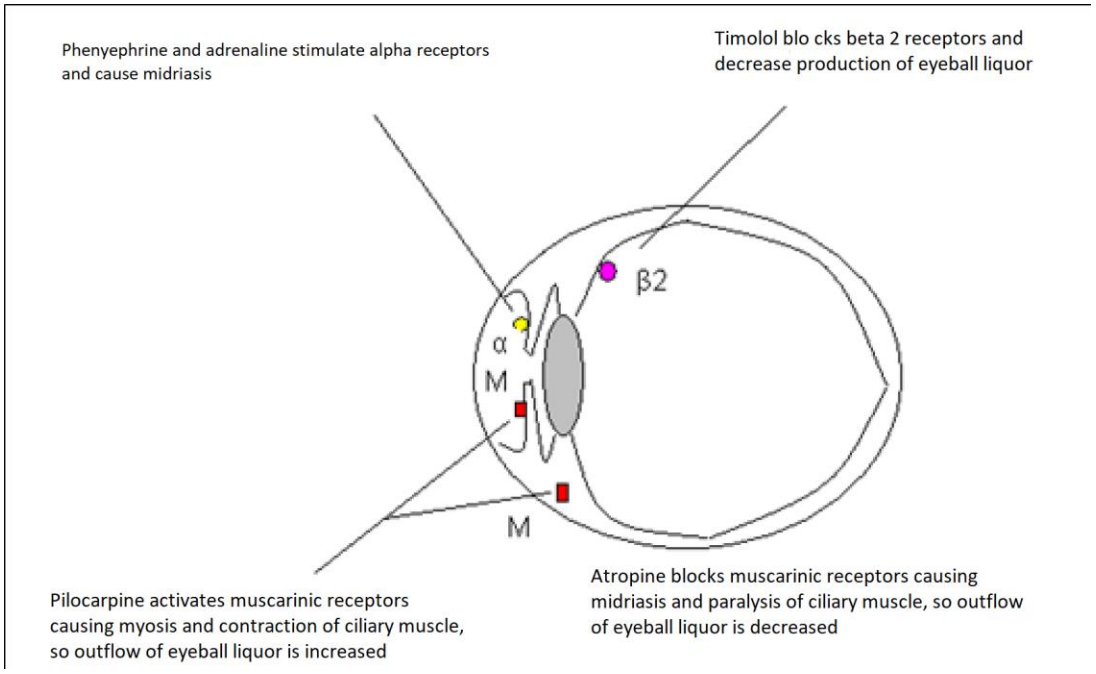


In the eye, the parasympathicus causes miosis and spasm of accommodation (contracts the ciliary muscle). Both of these effects occur through the activation of muscarinic receptors.

The drug pilocarpine in the form of eye drops activates muscarinic receptors and causes miosis and spasm of accommodation, but due to the effect of pilocarpine, the outflow of the aqueous humor from the eye is facilitated, so pilocarpine is used to treat acute glaucoma (a disease characterized by a sudden increase in pressure in the eye, which is accompanied by severe pain due to stretching of the eyeball). On the other hand, atropine and homatropine block muscarinic receptors in the eye, causing mydriasis (dilation of the pupils) and paralysis of accommodation (but thereby making the outflow of the aqueous humor difficult, so in a patient with an otherwise elevated pressure in the eye, they can provoke an attack of acute glaucoma). We use atropine and homatropine as a preparation for the examination of the fundus, but also for alternately inducing mydriasis in inflammation of the front part of the eye, in order to prevent the formation of adhesions of the iris to the cornea or lens.

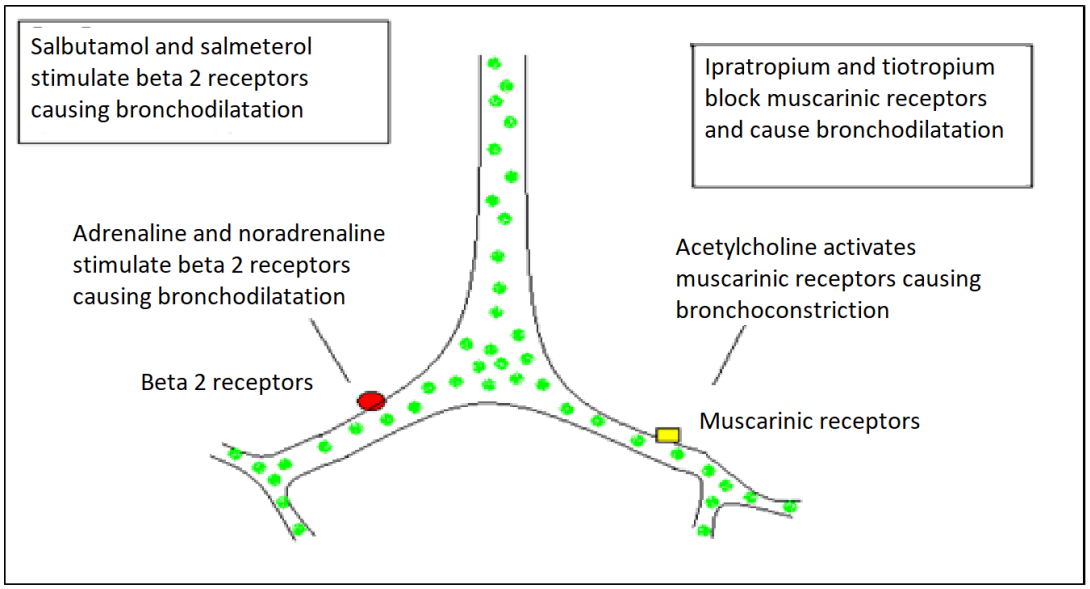
Sympathicus in the eye causes mydriasis and increases the production of aqueous humor. That is why we use the ß2 receptor blocker timolol in the treatment of chronic glaucoma.

Figure 3. Sympathetic and parasympathetic effects on the eye.



In the airways, the parasympathicus causes bronchoconstriction via M3 muscarinic receptors and the sympathicus causes bronchodilation via ß2 receptors. So we use the muscarinic receptor blocker ipratropium or tiotropium to induce bronchodilation. We also use ß2 agonists (short-acting salbutamol and long-acting salmeterol) to cause bronchodilation.

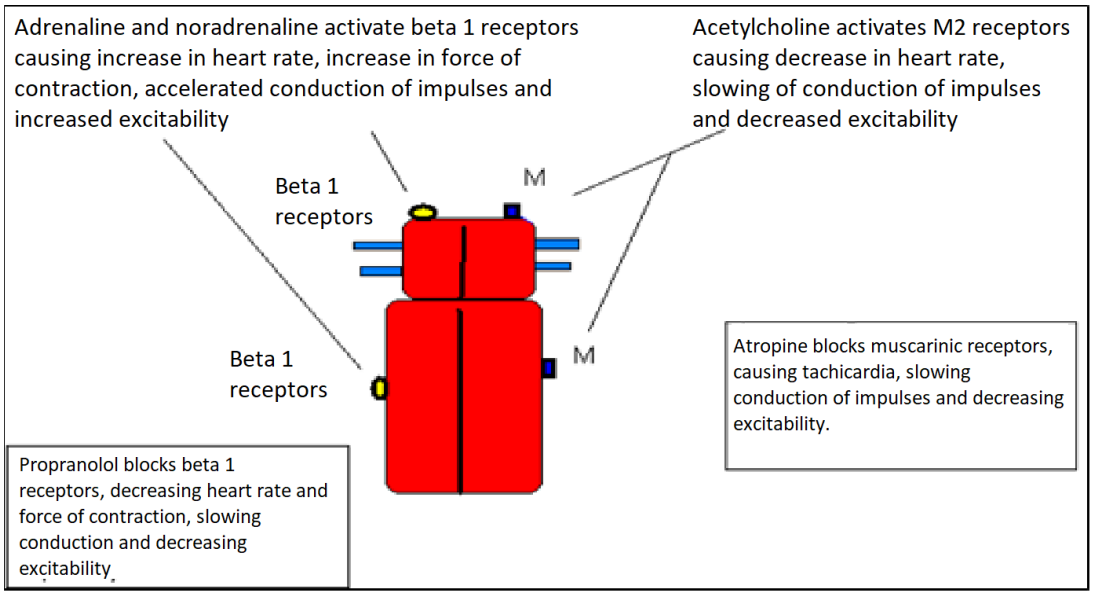
Figure 4. Sympathetic and parasympathetic effects on the bronchial tree.



The sympathicus in the heart causes an increase in the force of heart contraction, acceleration of the heart, acceleration of impulse conduction and greater excitability of the heart. All these effects are achieved by the sympathetic nerves through the activation of the β1 receptor. In case the heart's work is insufficient, for example, in case of cardiogenic shock, we can increase the heart's work by stimulating the ß1 receptor with dobutamine. On the other hand, with the help of ß blockers, we can reduce the heart's work and oxygen consumption, which is useful for the treatment of hypertension, heart failure, angina pectoris and arrhythmia. Most of the ß blockers we use are the non-selective blocker propranolol and the ß1 selective blockers (metoprolol and bisoprolol).

The parasympathicus in the heart causes decrease of the heart rate, reduces the speed of impulse conduction and reduces irritability. The parasympathetic system has a weak effect on the force of heart contraction because it does not innervate the ventricles. The parasympathicus in the heart acts via muscarinic M2 receptors. With atropine, which blocks muscarinic receptors, we can speed up the heart rate if someone has bradycardia.

Figure 5. Sympathetic and parasympathetic effects on the heart.

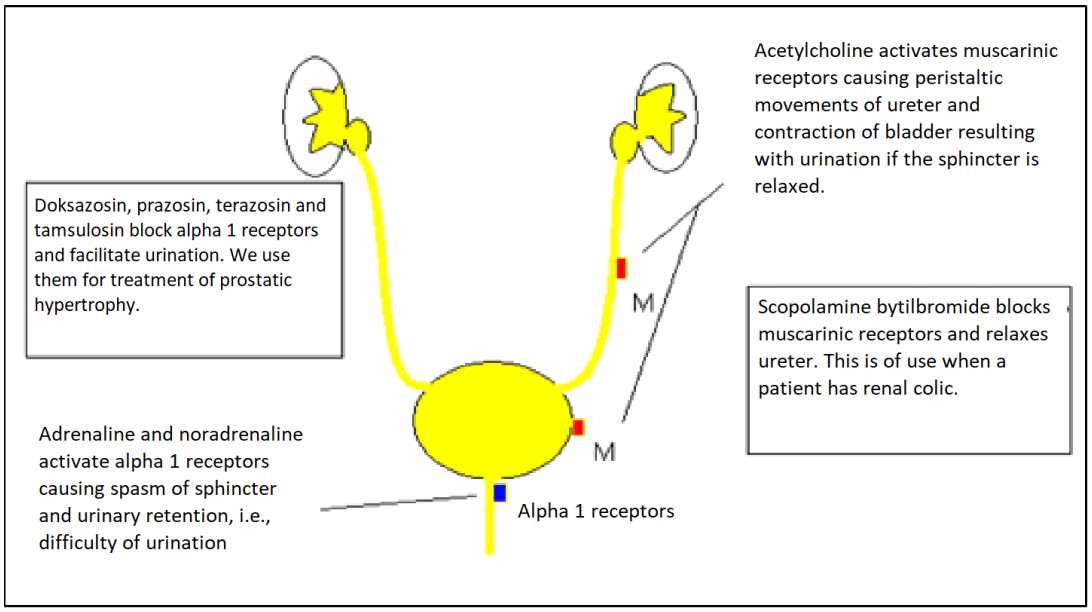


In the digestive tract, the parasympathicus accelerates peristalsis and increases gastric secretion by activating muscarinic receptors. Sympathicus leads to an increase in the tone of the sphincters in the digestive tract, due to their contraction after the activation of the alpha 1 receptor.

In the blood vessels of the internal organs and the skin, the sympathetic nerves cause vasoconstriction via the alpha 1 receptor. In the blood vessels of the extremities, the sympathetic nerves cause vasodilation via the ß2 receptor.

Sympathicus makes it difficult to urinate because it leads to a spasm of the urethral sphincter via the alpha receptor. That's why we give drugs that block alpha receptors to people with an enlarged prostate, so that patients can urinate more easily. Examples are the drugs prazosin, doxazosin and tamsulosin. The parasympathicus contracts the bladder via muscarinic receptors and accelerates urination.

Figure 6. Sympathetic and parasympathetic effects on the urinary tract.



Sympathicus acts on the pregnant uterus via ß2 receptors, causing relaxation. That is why we still occasionally use ß2 agonists (ritodrine) to prevent premature births.

Acetylcholine is broken down by acetylcholinesterase. If we block that enzyme with irreversible blockers (organophosphates, war poisons) or reversible blockers (neostigmine, physostigmine), we achieve the same state as when the parasympathicus is activated. We use neostigmine to accelerate intestinal peristalsis in paralytic ileus. Poisoning with organophosphates or war poisons is treated with atropine, which blocks muscarinic receptors, and pralidoxime, which liberates the enzyme from the poison.

Histamine receptor blockers are divided into H1 and H2 blockers. H1 blockers are primarily used to treat allergies and to prevent vomiting while driving (kinetosis). The first generation of H1 blockers has drowsiness and blockade of muscarinic receptors (anticholinergic effect) as side effects. Examples from this group of drugs are diphenhydramine, which is given orally, and chlorpyramine, which is administered intravenously. Second-generation H1 blockers do not cause drowsiness, but in some patients they can cause arrhythmia (e.g., loratadine), especially if used simultaneously with antibiotics from the macrolide group (erythromycin, clarithromycin, azithromycin) that inhibit their metabolism on cytochromes. H2 blockers reduce acid secretion in the parietal cells of the stomach and are therefore used to treat gastritis, peptic ulcers and gastroesophageal reflux. Nowadays, they are also used in critically ill hospital patients,

parenterally, in order to prevent the occurrence of stress ulcers in the stomach and bleeding from such ulcers. An example of a drug from this group is ranitidine.

Among the drugs that act through serotonin receptors, the most important are sumatriptan, which stops migraine attacks by activating 5-HT1_D receptors, and ondansterone, which is used to treat vomiting after the administration of cytostatics or postoperative vomiting, because it blocks 5-HT3 receptors in the vomiting center of the brain. The use of sumatriptan is risky for people suffering from angina pectoris, because it can cause spasm of the coronary arteries and provoke myocardial ischemia. Palonosetron, also a 5-HT3 receptor blocker, has a significantly longer duration of action than ondansetron, so it is used to prevent delayed vomiting after some types of cytostatics..

Anaphylactic reaction

Anaphylaxis is a severe systemic allergic reaction with a potentially fatal outcome. It begins suddenly, lasts no longer than 38 hours, affects one or more organ systems and creates one or more symptoms and signs: angioedema, stridor, dyspnea, hives, itching, vomiting or shock.

An anaphylactic reaction occurs due to the immune-induced release of mediators from mast cells and/or basophils, after exposure to an antigen to which the person was previously sensitized. Antigens are most often from insect venom, drugs, latex, from peanuts, from almonds, pistachios, from fish, eggs, milk and wheat.

Anaphylactoid reactions are clinically indistinguishable from anaphylactic reactions, but the IgE antibody-antigen reaction does not play a role in their occurrence, i.e. it is not an immunological mechanism of origin. Anaphylactoid reactions can occur after the administration of non-steroidal anti-inflammatory drugs, opioids or contrast agents in radiology.

Symptoms of an anaphylactic reaction usually appear after a few minutes of exposure to the allergen, but sometimes there is a latent period of one hour. About 80 percent of anaphylactic reactions end in one go, but in the remaining 20 percent there is a ***two-phase course***, i.e., the symptoms calm down after the application of the therapy, and then after (on average) around 10 hours (the range is from 1 to 38 hours), the symptoms reappear . In a third of patients, the second phase is more difficult than the first.

Table 1. Symptoms and signs of anaphylactic reaction.

Organ system	**A symptom or sign**
Nervous system	fainting, dizziness, rarely convulsions
Upper respiratory tract	sneezing, hoarseness, stridor, laryngeal edema, cough
Eye	itching, tears, redness
Lower respiratory tract	dyspnea, bronchospasm, tachypnea, cyanosis
Cardiovascular system	tachycardia, hypotension, arrhythmias, cardiac arrest, infarction
Skin	redness, itching, hives, angioedema
Gastrointestinal system	nausea, vomiting, diarrhea, abdominal pain

Treatment of anaphylactic reaction

The first drug to be administered when an anaphylactic reaction occurs is adrenaline, 0.3 - 0.5 mg ***intramuscularly*** (0.3 - 0.5 ml of dilution 1:1000). Subcutaneous application should be avoided, because absorption of the drug from the application site is unpredictable. Intravenous administration should be reserved only for severe anaphylactic shock, because such a route of administration is associated with a high risk of arrhythmias. If adrenaline is administered intravenously, it must first be diluted in a ratio of 1:10,000.

The dose of adrenaline for children is 0.01 mg / kg, up to a maximum of 0.3 mg. Doses of adrenaline in both adults and children can be repeated *every 10 minutes* , until the signs and symptoms of anaphylaxis disappear, or the adverse effects of the drug (palpitations, tremors, fear) occur.

Also, it is necessary to ensure the patency of the airways in patients , and apply oxygen. After adrenaline, the patient should be given blockers of histamine H_1 and H_2 receptors, diphenhydramine 50 mg and ranitidine 50 mg , intravenously. The combination of H_1 and H_2 antihistamines is more effective than the use of H_1 antihistamines alone. If the

patient has bronchospasm, it is useful to administer salbutamol (a beta-two receptor agonist) in the form of inhalation.

All patients with anaphylaxis should also be given corticosteroids (e.g., methylprednisolone, 125 mg intravenously, or 50 mg prednisone orally). They can prevent the second phase of an anaphylactic reaction. If patients are extremely hypotensive, they should be given 500 ml of saline intravenously.

If a patient with an anaphylactic reaction is on chronic therapy with beta-blockers or angiotensin-converting enzyme inhibitors, he/she will not respond well to adrenaline. Then glucagon should be applied, which does not act through beta-receptors, but has a chronotropic, inotropic and vasoactive effect, and causes the release of catecholamines from the nerve endings.

When the patient's condition improves, continue the treatment with antihistamines and corticosteroids for another four days. After the anaphylaxis has subsided completely, it is necessary to determine which antigen the patient is allergic to, in order to be able to avoid it in the future. This can be done with allergic skin tests and determining the presence of specific IgE antibodies.

Every patient who once experienced anaphylaxis should always have an auto-injector of adrenaline with them (special device, which resemble a pencil) and be trained to use it on themselves as soon as a new anaphylactic reaction occurs. In some countries, patients wear necklaces with a pendant, on which it is written that they are allergic to a certain antigen. In this way, doctors can effectively help them in the event that anaphylaxis occurs again.

EFFECTS OF ADRENERGIC AND ANTIADRENERGIC DRUGS IN THE ORAL CAVITY

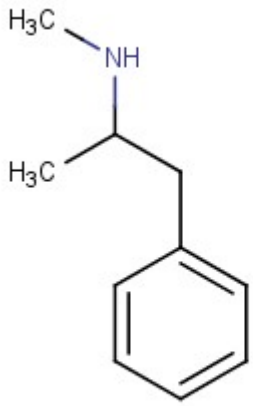
Of the adrenergic drugs in dentistry, adrenaline is used the most. Adrenaline can only be administered parenterally, because after oral administration it is quickly broken down by monoamine oxidase in the digestive tract. Adrenaline is usually **mixed in the same preparation with some local anesthetic,** so that when that mixture is injected near a tooth to be repaired or extracted (infiltration anesthesia) or near a nerve entering the mandible or maxilla (conduction anesthesia) the adrenaline causes vasoconstriction which slows down the removal of local anesthetic from the injection site. This prolongs the effect of the local anesthetic. Adrenaline is usually given together with local anesthetic lidocaine, bupivacaine or articaine.

When using adrenaline in this way, one should be careful if the patient is an old person or a person with a diseased heart. Adrenaline is still absorbed from the injection site and is carried to the heart by blood, where it can activate beta1 receptors, and lead to an acceleration of the heart and an increase in the force of its contraction. Such an effect increases the consumption of oxygen in the heart, so if a person has narrowed coronary arteries, a myocardial infarction may occur due to insufficient oxygen supply to the heart.

Adrenaline is also injected into the tissue of the oral cavity during surgical interventions with **profuse bleeding** . Due to the vasoconstriction caused by adrenaline acting on alpha receptors, bleeding decreases, so the surgeon has time to sew up the wound or perform the desired intervention.

If we inject adrenaline into the tissue of the oral cavity of a person who is under the influence of cocaine or amphetamine, it will be absorbed and reach the heart and blood vessels, where it will potentiate the effect of these two substances. There will be extremely strong stimulation of beta and alpha receptors, resulting with acceleration of the heart, strengthening of its contraction and a jump in blood pressure. If the patient has a history of coronary artery disease (narrowing of the coronary arteries), this overstimulation of the heart will lead to a heart attack.

Methamphetamine is an amphetamine derivative that is illegally made by "cooking" pseudoephedrine. On that occasion, a "dirty" preparation of methamphetamine is created with a lot of admixtures of corrosive substances: sulfuric acid, red phosphorus, lithium and others. When a person smokes methamphetamine, these corrosive substances are found in the smoke and deposited on the teeth and gums, corroding them.



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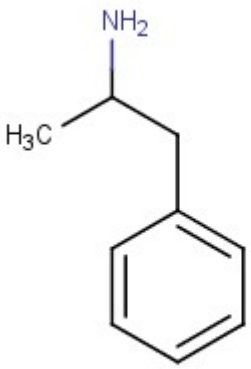


АМФЕТАМИН

Adrenaline should ***be used with caution in people who are on chronic therapy with non-selective beta-blockers*** . Since beta-2 receptors in the arteries of the extremities are blocked among others, adrenaline will not be able to cause vasodilation in those arteries, but only vasoconstriction in other arteries, leading to a significantly higher increase in blood pressure than in people who do not use beta blockers.

Adrenaline should also be avoided in combination with local anesthetics in dentistry in patients who are on chronic therapy with MAO inhibitors (moclobemide, tranylcypromine, iproniazid and others). MAO inhibitors are drugs that block the enzyme monoamine oxidase and thereby hinder the breakdown of catecholamines, including adrenaline. As a result of this blockage, adrenaline and noradrenaline accumulate, and arterial blood pressure may rise.

Patients taking alpha blockers (e.g., prazosin) or the central antihypertensives alpha-methyldopa or clonidine sometimes suffer from **postural hypotension,** because the sympathetic nervous system cannot adjust to the sudden drop in blood pressure upon standing. When standing up suddenly, such persons may experience reduced blood flow through the brain due to a drop in blood pressure, which results in a short-term loss of consciousness and a fall (so-called syncope). That is why people on chronic therapy with these drugs must gradually get up from the dentist's chair: first sit down and stay seated for about 15 seconds, and then stand up.

EFFECTS OF CHOLINERGIC AND ANTICHOLINERGIC DRUGS IN THE ORAL CAVITY

Cholinergic drugs in the oral cavity stimulate the secretion of saliva, which is important in patients in whom the secretion of saliva is reduced, i.e., who have xerostomia ("dry mouth"). Xerostomia can occur as part of autoimmune diseases of the connective tissue, when the tissue of the salivary glands deteriorates (the so-called Sjegren's syndrome), and then the patient has difficulty speaking and swallowing solid food. Patients can be helped by the administration of **pilocarpine**, a direct agonist of muscarinic receptors, which will increase the secretion of saliva. Pilocarpine is used in the form of tablets of 5 mg, which are swallowed with a glass of water.

Medicines and poisons that **inhibit acetylcholinesterase** (organophosphate insecticides malathion and parathion, nerve warfare poisons sarin, soman and tabun, drugs

neostigmine and physostigmine) lead to the accumulation of acetylcholine and excessive stimulation of the salivary glands, which results in hypersalivation, i.e. excessive secretion of saliva.

On the other hand, **drugs that block muscarinic receptors** lead to decreased salivation and xerostomia. These are primarily atropine and scopolamine, but if drugs used for some special indications have a similar antimuscarinic effect, they also block muscarinic receptors. Tricyclic antidepressants, some typical antipsychotics, antihistamines, digoxin, disopyramide, furosemide, diphenoxylate and some antiparkinsonian drugs (biperiden, trihexyphenidyl) are known for their side effects of antimuscarinic activity and "dry mouth".

Due to the blockade of muscarinic receptors and the reduction of saliva secretion, atropine is used in the treatment of excessive hypersalivation in the case when some reconstructive intervention in the oral cavity needs to be performed, and excessive secretion of saliva interferes with the work. Then it is enough to give the patient a tablet of 0.4 mg of atropine 1 hour before the intervention, and saliva secretion will almost completely stop.

CENTRAL NERVOUS SYSTEM (CNS)

SEDATIVES AND HYPNOTICS

Sedatives are drugs that slow down and alleviate the reaction of the person taking them to stressful stimuli from the external environment. Although sedatives in larger doses can put the person who uses them to sleep, after waking up there is a hangover that is quite unpleasant. For this reason, drugs were created that primarily facilitate falling asleep and prevent premature awakening; we call such drugs hypnotics. Today we still use two types of sedatives: benzodiazepines and barbiturates. Both groups act through receptors for GABA (gamma-aminobutyric acid), by facilitating the action of this amino acid, which is an inhibitory neurotransmitter in the central nervous system. GABA acts on two types of receptors, A (chlorine ion channel) and B (potassium ion channel), and after their activation causes hyperpolarization of the cell membrane and inactivation of the cell. Benzodiazepines increase the frequency of GABA type A receptor opening, and barbiturates increase the time that receptor is open. Due to the different mechanism of action, benzodiazepines, even in the highest doses, cannot lead to the death of the patient due to cessation of breathing, while barbiturates can. Precisely because of this difference and greater safety, today we only use benzodiazepines as sedatives and hypnotics. Of the benzodiazepines, we mostly use diazepam, which has a long effect (more than a day) and lorazepam, which has a shorter effect (about 6 hours). Because they are addictive, benzodiazepines should not be used for

more than three weeks. Benzodiazepines should never be mixed with alcohol because alcohol increases their depressant effect on the brain, until breathing stops. Of the barbiturates, we mostly use phenobarbitone, not as a sedative, but for the treatment of epilepsy, and thiopentone-sodium, for introducing the patient to general anesthesia intravenously.

Of the drugs that stimulate the CNS, today we mostly use methylxanthines (caffeine, theophylline and theobromine). These drugs stimulate adenosine receptors, and inhibit phosphodiesterase, which causes the accumulation of cAMP (cyclic adenosine monophosphate). Caffeine is used to treat apnea (stopping of breathing) in newborns and infants, which is caused by the immaturity of the nervous system. Theophylline is a useful bronchodilator, which was widely used in the treatment of bronchial asthma and chronic obstructive pulmonary syndrome, but in recent years due to its pronounced stimulating effect on the heart (it speeds up the heart's work and increases oxygen consumption in the myocardium, so it can provoke ischemia if the patient has coronary disease) methylxantines gave way to other drugs, which are administered mainly by inhalation. Theobromine is never used as a medicine, but is found in many teas and energy drinks intended to maintain alertness.

ANTIPSYCHOTICS

Antipsychotics are drugs that suppress the symptoms of psychosis, primarily the so-called "positive" (disorders of cognition and perception), and to a lesser extent "negative" symptoms (withdrawal into oneself, loss of interest in the environment). Antipsychotics are divided into typical (first generation) and atypical (second generation). Both work by blocking dopamine receptors in the brain, with the most important antipsychotic effect being the blocking of D2 dopamine receptors. In addition, atypical antipsychotics also block serotonin 5-HT_2 receptors, which is why they are more active in the sphere of "negative" symptoms.

Almost all antipsychotics cause hyperprolactinemia and increased appetite as side effects, but typical antipsychotics also cause motor disorders (a condition similar to parkinsonism, involuntary muscle spasms, etc.), while atypicals cause less motor and more metabolic disorders (obesity, hyperlipidemia, hyperglycemia). Of the typical ones, haloperidol and chlorpromazine are most often used, and of the atypical ones, risperidone, aripiprazole, clozapine and olanzapine. When an antipsychotic is prescribed, in principle only one drug is used, because the combination of antipsychotics does not have a stronger effect than monotherapy, while side effects are much more common.

Haloperidol has a special place in medicine and dentistry, because in addition to the treatment of psychosis, it is successfully used to calm delirious patients (persons who are not oriented in time, space and towards other people, and are also psychophysically restless, even aggressive), as an intravenous injection. The patient receives 5 milligrams of haloperidol intravenously every two hours, until he/she calms down (the maximum daily dose is 20 milligrams).

ANTIDEPRESSANTS

Antidepressants are drugs used to treat psychotic depression, panic disorder and many phobias (e.g., social phobia). All antidepressants begin to work clinically only after a latent period of 2-3 weeks, and can be classified into four groups according to the mechanism of action:

1) **Tricyclic antidepressants** (the most important representatives are amitriptyline and imipramine), which enhance noradrenergic transmission in the brain and act very effectively in the treatment of depression. However, they have a pronounced side effect on the heart (proarrhythmogenic effect) and an antimuscarinic side effect (dry mouth, constipation, urinary retention, increased intraocular pressure, tachycardia).

2) **Serotonin uptake blockers**, which work by enhancing serotonergic transmission in the brain. The most important representatives are: paroxetine, citalopram and sertraline. They are better tolerated than tricyclics (they are not proarrhythmogenic or anticholinergic), so today they are the drugs of first choice in the treatment of depression. However, they can sometimes cause serious side effects such as bleeding from the gastrointestinal tract, hyponatremia or serotonin syndrome (fever, muscle spasms, disturbances of consciousness).

3) **Heterocyclic antidepressants** are drugs with mixed properties of tricyclics and serotonin reuptake blockers. Among them, trazodone and nefazodone have a hypnotic effect in addition to an antidepressant, and venlafaxine and mirtazapine (this last drug also has a hypnotic effect, and unlike serotonin reuptake blockers, it increases appetite).

4) **Monoamine oxidase inhibitors (MAO)**, which work by preventing the breakdown of noradrenaline by monoamine oxidase. Moclobemide, which is selective for the MAO-A subtype of the enzyme, is most commonly used today. When patients take MAO inhibitors, they must not simultaneously use other antidepressants, drugs that are sympathomimetic and foods containing tyramine (old cheese, wine) because a hypertensive crisis may occur. It is interesting that one of the modern antibiotics, linezolid, also acts as an MAO inhibitor, so simultaneous use of that drug with antidepressants should be avoided.

Similar to antipsychotics, antidepressants are used as monotherapy, that is, they are not combined, except in exceptional situations. If we want to stop the use of antidepressants, it is done gradually, by reducing the dose over several months. Otherwise, sudden discontinuation of antidepressants can cause withdrawal syndrome (anxiety, depression, irritability, etc.).

PSYCHOSTABILISERS

Psychostabilizers are drugs that prevent excessive mood swings in patients with bipolar disorder (manic-depressive psychosis). Lithium carbonate is still primarily used for this purpose, but if patients cannot tolerate this drug, some antiepileptics can be used (primarily valproic acid, but also lamotrigine, carbamazepine or topiramate). Lithium carbonate has a lot of side effects (damage to kidney tubules, thyroid gland, appearance of acne on the skin of the face, tremors), so its concentration in the blood must be measured. People on lithium therapy must be very careful about the intake and loss of sodium: since the lithium ion has similar characteristics to the sodium ion, in case of insufficient intake or increased loss (e.g., diarrhea, use of strong diuretics) lithium will enter the cells instead of sodium during depolarization of the membrane, so its toxic effects will be more pronounced.

ANTIEPILEPTIC DRUGS

Antiepileptic drugs prevent or stop epileptic seizures. Most antiepileptic drugs are used to prevent seizures, while seizure termination is carried out by intravenous benzodiazepines, such as diazepam, lorazepam or midazolam. At the same time, it should be remembered that every epileptic attack should not be stopped with drugs, because most of them will pass spontaneously, without consequences for the patient (it is enough to place the patient in a place where he will not be injured). The attack is stopped only if it lasts longer than 5 minutes, because then due to insufficient oxygenation and intense contractions, acidosis and damage to the striated muscles can occur, and even kidney failure if too much myoglobin is released from the muscles and clogs the kidney tubules.

Medicines that prevent epileptic seizures are chosen based on the type of epilepsy the patient has. At first, seizure control is always tried with only one drug, and if it fails, patients often take two or even three antiepileptic drugs at the same time. Unfortunately, despite combined therapy, about 30% of patients have drug-resistant epilepsy, i.e., the frequency of attacks cannot be reduced.

Carbamazepine, phenobarbitone, valproic acid, lamotrigine, topiramate and levetiracetam are used for the treatment of generalized epilepsies other than absence, as well as for the treatment of focal onset (partial) epilepsies. For the prevention of the absance (the patient only loses consciousness, there are no contractions or loss of muscle tone), we use ethosuccimid or valproic acid.

Since antiepileptic drugs have a narrow therapeutic range, it is necessary to periodically measure the concentration of antiepileptic drugs in the blood in order to prevent the occurrence of toxic effects and to see if the antiepileptic drug is working, that is, if the patient is taking the drug at all. The use of antiepileptic drugs must not be stopped suddenly, because the patient may fall into status epilepticus. When we prescribe another drug to a patient who is on antiepileptic drugs, we have to check whether it interacts with antiepileptic drugs, because they are known for undesirable interactions. Especially carbamazepine, phenobarbital and phenytoin often interact, because they accelerate the metabolism of other drugs on cytochrome 3A4, and thus lower their concentration in the blood.

OPIOIDS

Opium is the resin that oozes from unripe opium poppy pods after they are cut with a special knife. This resin contains morphine, noscapine and codeine, slightly alkaline substances that are therefore called alkaloids. Morphine, noscapine and codeine activate special opioid receptors on the nerve pathways that transmit the sensation of pain, inhibiting those pathways and preventing us from becoming aware of pain. Apart from the mentioned natural substances, there are many synthetic compounds that act in the same way, so all such substances are called opioids under one name. Opioids are still the strongest painkillers (analgesics) available today.

Morphine was the first opioid to come into use, and is still the most widely used of all opioids. Mofin can be administered parenterally and orally, and we use it to suppress the most severe pain, whether it arises acutely (e.g., pain after a large bone fracture) or chronically (cancer pain). In addition to morphine, we often use **oxycodone (oral), methadone (oral), and fentanyl (transdermal patch)**. A special group of opioids consists of the so-called partial agonists, i.e. drugs that stimulate opioid receptors to a lesser extent than the previously mentioned opioids (which are also called "full agonists") and also affect other receptors: **meperidine, pentazocine, butorphanol and tramadol**. Partial agonists have a weaker effect on pain than full agonists, and due to their effect on other receptors, they often cause nightmares, confusion and perception disorders in patients.

The greatest danger with the use of opioids is respiratory depression that occurs if they are overdosed or if the patient already has weakened respiratory function. That's why when we administer these drugs we have to control the patient's breathing. If the number of respirations per minute is less than 8, the opioid dose should be reduced immediately. Another problem with the use of these drugs is that they are addictive, so there is a high tendency for abuse. Otherwise, opioids cause other side effects, of which constipation is the most common. A characteristic sign that someone is on opioid therapy is very narrow pupils, because opioids cause marked miosis.

In the event that the patient was overdosed on opioids, and is in danger of stopping breathing, it can be helped by intravenous administration of naloxone, a drug that blocks opioid receptors.

ADDICTIVE DRUGS

As already mentioned, opioids are addictive in a person who takes them for a long time. Addiction occurs due to habituation of cells of the nervous system to the constant presence of a drug that stimulates opioid receptors, which gradually reduce the number of their receptors. If the administration of opioids is stopped suddenly, the neurons are suddenly left without sufficient activation of opioid receptors, and a set of symptoms (restlessness, muscle spasms, cold and prickly skin, nasal discharge) appears, which we call withdrawal syndrome. The withdrawal syndrome can be terminated by re-administration of one of the opioids; otherwise, without treatment, the abstinence syndrome passes in 7 days.

In addition to opioids, other drugs with an effect on the central nervous system can cause addiction, the most important of which are alcohol, sedatives, stimulants (cocaine, amphetamine) and hallucinogens. With most of these drugs, when the application is stopped suddenly, an abstinence syndrome occurs, sometimes milder (with stimulants), sometimes more severe (with alcohol). Exceptionally, when hallucinogens are stopped, there is no withdrawal syndrome. If we want to rid the patient of addiction and avoid the occurrence of abstinence syndrome, the principle of treatment is as follows: the drug that causes addiction is replaced by a drug from the same group that has a significantly longer effect, and then the dose of that new drug is gradually reduced (over several weeks).

NON-STEROID ANTI-INFLAMMATORY DRUGS

Medicines that do not have a steroid structure (the structural formula does not have a steroid nucleus that cholesterol, corticosteroids and sex hormones have), and work by reducing inflammation in tissues, are called non-steroidal anti-inflammatory drugs. The mechanism of action of these drugs is the inhibition of cyclo-oxygenase and, therefore, the prevention of prostaglandin synthesis. There are two cyclooxygenases: type 1 and type 2. Due to the blockade of cyclooxygenase type 2, the desired effects of these drugs mainly occur: anti-inflammatory (reduce inflammation), analgesic (reduce pain) and antipyretic (reduce body temperature). Due to the blockade of cyclooxygenase type 1, there are mainly unwanted effects: damage to the gastric mucosa with the appearance of bleeding from the stomach, damage to kidney function with long-term use, myocardial infarction, heart failure, stroke and delay in childbirth if used in late pregnancy. All drugs from this group can worsen bronchial asthma, because due to the blockade of prostaglandin formation, larger amounts of leukotrienes are produced, which lead to bronchoconstriction. Also, some of the drugs from this group, including diclofenac, can worsen the condition of patients with heart failure, so they should be avoided in such patients.

The most important drugs from this group are: acetylsalicylic acid, diclofenac, ibuprofen and ketorolac. Of all the drugs in this group, only acetylsalicylic acid irreversibly inhibits cyclooxygenase, which allows it to act in small doses as an anti-aggregation agent (prevents the deposition of platelets and the formation of thrombus in arterial blood vessels). In an effort to create non-steroidal anti-inflammatory drugs that would not have unwanted effects, selective cyclooxygenase 2 blockers were synthesized, of which celecoxib is still used today. Unfortunately, even with the use of selective blockers, the listed side effects are not completely eliminated.

DRUGS FOR THE TREATMENT OF GOUT

Gout is caused by increased production of uric acid in the body. Uric acid accumulates in the joints (especially in the big toe joint) and causes pain and inflammation. A gout attack is usually provoked by drinking alcohol. A gout attack is interrupted by the administration of small doses of colchicine, which prevents the movement of leukocytes. A gout attack is prevented by the use of allopurinol or febuxostat, which prevent the synthesis of uric acid, or by the use of probenecid, which increases the excretion of uric acid. Colchicine is a very toxic substance (it causes the failure of almost all vital organs), but here it is administered in subtoxic doses, so it is well tolerated (sometimes it causes nausea and

abdominal pain). If colchicine is not available, non-steroidal anti-inflammatory drugs are used.

PARACETAMOL

Paracetamol is an old drug that, unlike non-steroidal anti-inflammatory drugs, acts only as an analgesic and antipyretic. It is suitable for use during pregnancy to treat pain and fever because it does not harm the fetus. It is also an excellent choice for treating pain and fever in people with stomach ailments, as it does not irritate the mucous membrane. It can be applied both orally and parenterally.

It is important not to use more than 4 grams of paracetamol per day. If overdosed, a toxic benzoquinone metabolite is formed in the liver, leading to liver necrosis. To prevent this, we give a patient overdosed with paracetamol the antidote acetylcysteine, which neutralizes the toxic metabolite by binding reactive oxygen groups to its SH radicals.

APPLICATION OF ANALGESICS IN DENTISTRY

After the local anesthesia wears off (about one to two hours after the intervention), the patient should be allowed to relieve the pain using analgesics. It is best for the patient to take the analgesic immediately after the intervention, while the local anesthesia is still working, because then after the anesthesia wears off, its effect on pain reduction will be full, so the patient will not feel pain.

It is best to use one of the non-steroidal anti-inflammatory drugs (e.g., ibuprofen in a dose of 600 mg every 8 hours) or paracetamol (if the patient has a stomach disease, in a dose of 500 mg every 6-8 hours) for analgesia in dentistry. These medicines should be used for a maximum of three days. After that period, if the pain still exists, it means that a complication has occurred, which should be solved in some other way, not with analgesics. Further application of analgesics will only mask a potentially dangerous condition, which must be urgently addressed.

In the case of toothache caused by some process on the tooth, we give analgesics only temporarily, while the patient waits for intervention and receives antibiotics, for example. In such situations, the choice of analgesics is the same as for pain control after interventions.

Adverse effects of analgesics in the oral cavity

Out of the non-steroidal anti-inflammatory drugs, only aspirin should be avoided in dentistry. The reason for this is its unique property of interfering with the aggregation of platelets, thereby increasing the tendency to bleed. After an intervention that is accompanied by bleeding, it can be increased if the patient is under the influence of aspirin. Therefore, aspirin should not be used as an analgesic in dentistry, and if the patient is already using it, he should be advised to stop using it the day before the operation (of course, if the risk of thrombosis does not increase excessively after discontinuation of aspirin).

A very rare side effect that can occur after the use of any analgesic is the appearance of blisters on the lips and superficial ulcers in the oral cavity. These changes are part of the Stevens-Johnson syndrome, which also includes the appearance of a large number of blisters all over the skin, which burst easily, leaving a bare surface from which lymph drains. The dentist should know that such a condition is potentially life-threatening, and that the patient should be referred to a doctor immediately.

NEUROMUSCULAR BLOCKERS

This group includes drugs that bind to nicotinic receptors in striated muscles, block them, and thus lead to muscle paralysis. There are two types:

1) **Depolarizing neuromuscular blockers**, which first cause smaller, uncoordinated muscle contractions (fasciculations) and then paralysis. A representative is succinyl-choline. Its effect is short, 5-10 minutes, because it is broken down by acetylcholinesterase.

2) **Non-depolarizing**, which only block nicotinic receptors and immediately lead to paralysis. Rocuronium and vecuronium from this group of drugs are the most used today. The effect of non-depolarizing blockers lasts longer than that of succinylcholine, about thirty minutes to an hour. In case we need to terminate the action of non-depolarizing blockers earlier, we can do so by intravenous administration of neostigmine, which, due to the blockade of acetylcholinesterase, causes the accumulation of acetylcholine and competitive displacement of the blockers from nicotinic receptors.

We use succinyl-choline only to put the patient under anesthesia (to enable endotracheal intubation), and non-depolarizing blockers for muscle relaxation during general anesthesia, so that the surgeon can perform the operation without resistance from the patient's musculature.

LOCAL ANESTHETICS

Local anesthetics are drugs that block sodium ion channels in nerve fibers and thus prevent the transmission of impulses, i.e., conveying the sensation of pain. There are two groups of local anesthetics: esters (procaine, tetracaine) and amides (lidocaine, benzocaine, articaine). We use local anesthetics for tooth extraction or minor surgical interventions by injecting them around the site of the intervention (infiltration local anesthesia) or near the nerve that innervates that site (conducting local anesthesia). After applying the local anesthetic, you should wait 5 to 10 minutes for their effect to start, i.e., to lose the feeling of pain. If the local anesthetic is injected by itself, the effect usually lasts about 30 minutes, which is sometimes not enough to perform the intervention. That is why preparations are usually used in dentistry that contain adrenaline in the same ampoule along with a local anesthetic. Adrenaline causes vasoconstriction at the site of application, which slows the absorption of the local anesthetic and allows it to stay longer and work longer where it was applied. After administration of local anesthetic preparations with adrenaline, anesthesia lasts 60-90 minutes.

Consequences of overdose of local anesthetics

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. Fortunately, there is no cross-allergy between amides and esters; if someone is allergic to an ester local anesthetic, he/she 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 levobupivacaine or its chemical analogue ropivacaine, are increasingly being used instead of bupivacaine.

Principles of application of local anesthetics in dentistry

Local anesthetics are injected near the nerves that innervate the teeth, depending on the tooth being repaired or extracted. After 5-10 minutes, the anesthetic starts to work, and the intervention can begin. Usually, the local anesthetic is in the same ampoule with adrenaline, which causes vasoconstriction, slows down the absorption of the anesthetic from the site of application, and thereby prolongs the effect of the anesthetic. The ampoules must then also contain sodium meta-bisulfite, a reducing agent that prevents adrenaline from oxidizing and losing its effect. The effect of local anesthetics usually lasts 30-60 minutes.

If a local anesthetic is injected near one of the above-mentioned nerves, it is called conduction anesthesia (because the entire area innervated by that nerve, i.e., from which it carries information about pain to the brain, will become insensitive); if it is applied to the tissue or to the tooth being repaired, it is called infiltration anesthesia. Finally, application of anesthetic in the form of a spray or by smearing on the mucous membrane is called superficial anesthesia.

Possible complications of local anesthesia in dentistry are: spread of infection (that's why they are not used in infected tissue), hematoma (if an arterial blood vessel is injured by a needle), nerve injury, facial nerve blockage by mistake, endocarditis (due to bacteria entering the blood during injection). and the occurrence of arrhythmias in people with heart disease.

GENERAL ANESTHETICS

General anesthetics are drugs that lead to depression of the CNS so that a person under their influence loses consciousness, does not feel pain, touch, and cannot move. The goal of general anesthesia is that the depression of the CNS is deep enough to achieve the aforementioned, while the vital centers (respiratory center and cardiovascular center in the medulla oblongata) work smoothly. The effect of anesthetics is realized gradually, as their concentration in the brain tissue increases: in the first phase the patient is still conscious, he just does not feel pain, in the second phase the patient becomes restless but loses consciousness, in the third phase he/she is unconscious with relaxed muscles and does not

react to external stimuli. In the third phase, surgical interventions are performed. If general anesthetics are overdosed, the fourth phase occurs, i.e., depression of the respiratory center and the cardio-vascular center in the medulla oblongata due to which the patient dies. According to the method of administration, general anesthetics can be divided into intravenous and inhalation.

Intravenous anesthetics work for a short time (about 10 minutes) and are only used to introduce the patient to general inhalation anesthesia or for short interventions. Thiopentone sodium and propofol are mostly used for induction of anesthesia, and midazolam for minor interventions. Since thiopentone sodium and propofol tend to lead to hypotension and depression of the vital centers if given in large doses, ketamine is used for general intravenous anesthesia in children and the elderly, which even slightly raises blood pressure.

Inhalation anesthetics are administered in the form of gas or vapor through the airways. Nitrogen suboxide is the most frequently used gas, and sevoflurane, halothane and enflurane are the most frequently used vapors. Inhalation anesthetics are used to maintain general anesthesia. They enter the body through the airways and lungs and exit the same way when we stop applying anesthesia, using in both cases the concentration gradient as a driving force. Since general anesthetics by themselves do not have an analgesic effect, opioid analgesics are added to the patient during general anesthesia, most often fentanyl or its derivatives alfentanil or sufentanil. The mentioned general anesthetics in the form of vapor have as an unwanted effect the occurrence of ventricular arrhythmias in the heart, so anesthesiologists must take special care of this.

PHARMACOLOGY OF THE CARDIOVASCULAR SYSTEM

ANTIHYPERTENSIVES

Hypertension is divided into: pre-hypertension (diastolic pressure up to 90 mm Hg and systolic pressure up to 140 mm), stage I hypertension (diastolic 90-100 mm, systolic 140-160 mm) and stage II hypertension (higher pressure values than 100 mm diastolic and 160 mm systolic). Prehypertension can only be treated with hygienic dietary measures (the patient should lose weight, walk more, should not add salt to food, should stop smoking and alcohol use). Stage I hypertension must be treated with drugs, but only after examining the

cause of the hypertension. For stage I hypertension, we can give one drug from the following groups of drugs:

1) **Beta 1 (ß1) selective blockers** - we give them mostly to younger patients - examples of beta 1 (ß1) selective blockers are metoprolol and bisoprolol.

2) **Angiotensin-converting enzyme inhibitors (ACE inhibitors)**, for example captopril, enalapril, ramipril, lisinopril, quinapril and others. ACE-inhibitors block convertase, i.e., the enzyme that creates angiotensin 2. ACE-inhibitors work best in people whose hypertension is of renal origin (e.g., nephropathy in diabetics, hypertension in renal failure). These drugs must be introduced to the patient gradually, starting with the lowest effective dose, which is then increased over several weeks to the optimal dose. If they were introduced suddenly, in the maximum dose, the patient would experience excessive hypotension, which could cause him/her to faint and injure himself. In addition, some patients do not tolerate these drugs because they cause a persistent dry cough (due to the blockade of convertase, which normally also breaks down bradykinin, there is an accumulation of this inflammatory mediator in the respiratory tract, inflammation and nerve irritation). In such patients, we replace ACE inhibitors with drugs that inhibit receptors for angiotensin 2 (valsartan, irbesartan and others). In addition to the already mentioned side effects, ACE-inhibitors tend to lead to hyperkalemia.

3) **Diuretics** are drugs that increase urine output. In the treatment of hypertension, we use thiazide diuretics (hydrochlorothiazide, polythiazide), which can increase urine output by 2-3 liters per day at most. When treating hypertension, we use thiazide diuretics in smaller doses than when we use them for the treatment of edema, so then they do not show unwanted effects. When thiazide diuretics are used in larger doses to treat edema, they cause hypokalemia and can worsen diabetes and gout. Loop of Henle diuretics (furosemide, ethacrynic acid), which can increase urine output up to 10 liters per day, are used to treat hypertension only in patients with kidney failure, because such patients do not respond to thiazide diuretics. Loop of Henle diuretics have the same side effects as thiazide diuretics (hypokalemia, worsening of diabetes and gout).

4) **Calcium channel blockers** lead to a decrease in arterial blood pressure due to dilation of the arteries. Amlodipine and nifedipine are mostly used in the treatment of hypertension.

In patients with hypertension in stage I, we initially use one of the drugs from the mentioned groups, choosing on the basis of possible side effects, possible added positive effects and patient characteristics (e.g., patients with hypertension and diabetes must be given an ACE-inhibitor, because apart from regulating pressure it slows down the development of nephropathy; we do not give large doses of beta-blockers to elderly patients,

because they can worsen heart failure, etc.). If hypertension is not controlled with one drug, then we give a combination of two or three drugs from different groups.

Hypertension in stage II is treated with the use of strong antihypertensives (so-called second-line antihypertensives):

1) **Selective alpha blockers due to blockade of alpha 1 (α1)** receptors lead to strong vasodilation, which significantly lowers blood pressure. A problem with the use of this group of drugs can be reflex tachycardia (although it occurs less often than with non-selective alpha blockers), i.e., the drop in pressure causes the activation of baroreceptors in the aortic arch and carotid sinus, and, by reflex, accelerates the heart rate. Prazosin, terazosin and doxazosin are the most commonly used drugs from this group.

2) **Central antihypertensives (alpha methyldopa, clonidine)** due to stimulation of presynaptic alpha 2 receptors in the central nervous system reduce the release of neurotransmitters, thus reducing the activity of the entire sympathetic nervous system. Due to reduced sympathetic activity, vasodilatation and slowing down of the heart occur, which results in a drop in blood pressure. In men, these drugs lead to ejaculation disorders, and in patients of both genders, alpha-methyldopa can lead to hemolytic anemia (therefore, it is necessary to monitor the blood count periodically), while clonidine, in case of a sudden interruption of administration, can cause an extreme rise in pressure.

A sudden increase in blood pressure (over 160/110 mm Hg) is called a **hypertensive emergency.** If the patient with this increase in pressure has no neurological symptoms (paralysis, loss of consciousness, or similar), then we can let him swallow on the field or in the clinic calcium channel blocker - nifedipine in the form of a delayed-release tablet of 20 mg, or one tablet of 50 mg of captopril. This type of therapy will lead to a gradual normalization of blood pressure in the next few hours. In the past, there was a wrong practice of intravenous administration of vasodilators (e.g., diazoxide) and sudden lowering of pressure, which could lead to death due to myocardial ischemia. If the patient has a sudden increase in blood pressure and neurological symptoms, it is a real hypertensive crisis, and then after oral administration of nifedipine or captopril, he/she must be urgently transported to the hospital where treatment continues with slow intravenous administration of vasodilators such as sodium nitroprusside.

DIURETICS

As already mentioned, diuretics are drugs that increase the amount of urine excreted per unit of time. There are five main groups of diuretics:

1) **Thiazide diuretics** act on the distal tubule where they interfere with the reabsorption of Na+ and Cl-. Due to the increased loss of Na+, at the end of the distal tubule, Na+ is reabsorbed more and more K+ is expelled instead. Therefore, the main complication of the use of these diuretics is hypokalemia. Representatives of this group are hydrochlorothiazide and polythiazide. The so-called "thiazide-like diuretics" are also used, which have a different molecular structure, but the same mechanism of action (kinetazone, metolazone). Thiazide and similar diuretics can at most increase urine output by about 2-3 liters per day. They are used for the treatment of edema in chronic heart failure, and in half the doses for the treatment of hypertension. In addition to hypokalemia, they also cause hyperglycemia and hyperuricemia.

2) **Loop of Henle diuretics** act on the thick arm of the loop of Henle where they prevent the reabsorption of Na+, K+ and Cl-. This effect results in increased loss of K+ and hypokalemia. The main representatives are furosemide, bumetanide and ethacrynic acid. These are powerful diuretics that can increase urine output by 10 liters per day. They are used to treat larger edemas in heart failure, pulmonary edema, and to treat edema and hypertension in renal failure, because thiazide diuretics do not work in hypofunctioning kidneys. In addition to hypokalemia, these drugs cause hyperglycemia and hyperuricemia. Because loop of Henle diuretics increase Ca++ excretion, they are also used to treat hypercalcemia in malignant diseases, along with saline infusion. Loop of Henle diuretics should not be used to treat hypertension, because their side effects are more pronounced than those of thiazide diuretics. Their intravenous administration should be slow, otherwise hearing damage may occur.

3) **Osmotic diuretics** are drugs that, after filtration in the glomeruli, are not reabsorbed from the tubules, but take water with them due to the effect of the principle of osmosis. The main representative is mannitol. Osmotic diuretics are used only short-term for the treatment of brain edema after injuries and elevated intraocular pressure in acute glaucoma. In these states, they draw water from the brain and eye, and then draw it through the kidneys into the urine. When using these drugs, there is a risk of acute pulmonary edema, because the volume of extracellular fluid increases, so they must be dosed carefully.

4) **Potassium-sparing diuretics** increase diuresis, not leading to loss, but to retention of potassium ions in the body. There are two types of these diuretics, one that blocks the action of aldosterone (representatives are spironolactone and eplerenone), and the other that interferes with the reabsorption of sodium ions and the excretion of K+ in the cells of the distal tubule of the kidney (in these cells, sodium ions are exchanged for potassium ions, so when there is no reabsorption of sodium, there is no excretion of potassium; representatives are amiloride and triamterene). Spironolactone and eplerenone are used to treat ascites and severe forms of heart failure. Amiloride and similar diuretics are used only in combination with thiazide diuretics to prevent K+ loss caused by thiazide diuretics. Potassium-sparing

diuretics must not be given together with ACE-inhibitors and drugs that block receptors for angiotensin, because both groups of drugs increase the level of K+ in the blood, so severe hyperkalemia can occur.

5) **Carbonic anhydrase inhibitors** are drugs that interfere with the reabsorption of bicarbonate in the proximal tubules. The representative of this group is acetazolamide. Its effect is lost after a few weeks of use, so today we do not use this group of diuretics.

CALCIUM CHANNEL BLOCKERS

Drugs from this group block calcium ion channels in the membranes of heart and vascular smooth muscle cells so that less Ca++ enters those cells. The consequence of their action in blood vessels is the relaxation of smooth muscle cells, that is, vasodilatation (primarily of arterial blood vessels). The consequence of blocking channels for Ca++ in the heart is a decrease in conduction velocity and a decrease in the force of cardiac contraction. Of the drugs from this group, verapamil acts more on the heart than on blood vessels, diltiazem acts equally on both the heart and blood vessels, and nifedipine and amlodipine act almost exclusively on blood vessels. That is why we use verapamil for the treatment of arrhythmias (atrial arrhythmias) and for the treatment of angina pectoris (especially vasospastic angina). We use nifedipine and amlodipine primarily for the treatment of hypertension. Diltiazem can be used for all of the listed conditions.

Calcium channel blockers have few side effects, but they should be avoided in people who are already receiving ß-blockers, so that their effect on the heart does not add up and A-V block occurs. Also, calcium channel blockers should not be used in people with heart failure, as studies have shown that the risk of death increases.

NITRATES

Nitrates work by releasing nitric oxide (NO) from their molecule, which then induces the formation of cyclic guanosine monophosphate (cGMP) and leads to relaxation of vascular smooth muscle. That's why nitrates lead to vasodilation of both arteries and veins, with veins dilating more than arteries. Of the nitrates, we use nitroglycerol to stop an attack of angina pectoris. Nitroglycerol is placed under the tongue by the patient so that the

medicine from the oral cavity reaches the heart faster and to avoid passing through the liver, because it is broken down so quickly there that no active medicine reaches the systemic circulation. The effect of nitroglycerol lasts only 20-30 minutes.

In addition to nitroglycerol, we use nitrates with a longer effect, the most important of which is isosorbide-mononitrate. The patient takes this medicine to prevent angina pectoris attacks. The problem with the use of nitrates is the occurrence of tachyphylaxis, that is, tolerance that develops quickly. In order to prevent the occurrence of tachyphylaxis, the patient takes these drugs in the morning and at noon and not in the evening, so that the body recovers overnight and becomes sensitive to nitrates again the next day. However, this creates a new problem: in the morning, immediately after waking up, while the patient has not yet taken the morning dose, the concentration of isosorbide mononitrate in the blood is so low that the patient can have an angina pectoris attack (this phenomenon is called the "zero hour effect"). Otherwise, the most common side effect of nitrates is headache due to the dilation of the blood vessels of the head and neck.

BETA BLOCKERS

By blocking beta receptors in the heart, drugs from this group prevent the excessive stimulating effect of sympathetic nerves on the heart, which is very useful in heart failure, hypertension, angina pectoris and arrhythmias. They can be non-selective, when they block ß1 and ß2 receptors, for example propranolol, and selective, which block only ß1 receptors in the heart, for example metoprolol and bisoprolol. Today, beta 1 selective blockers are primarily used (with the exception of the use of propranolol in arrhythmias), which, due to the blockade of ß1 receptors in the heart, reduce the force of heart contraction, reduce heart rate, reduce irritability and conduction speed. For the treatment of heart failure, beta 1 blockers are also used, which, in addition to the basic effect, also block alpha 1 receptors in the blood vessels, additionally reducing the burden on the heart (such a drug is, for example, carvedilol).

Non-selective beta-blockers can cause exacerbation of bronchial asthma or chronic obstructive pulmonary disease (COPD) due to blockade of ß2 receptors in the bronchi. As this can also happen with selective beta 1 blockers (because the selectivity is not absolute), these drugs should be avoided in patients with bronchial asthma and COPD. The use of beta-blockers is also risky in diabetics, because they can mask the signs of hypoglycemia, and also facilitate the occurrence of hypoglycemia, since they make it difficult to mobilize glucose from glycogen.

Warning!

Beta blockers and ACE-inhibitors are introduced into the patient's therapy gradually, that is, we start with the lowest dose and over several weeks increase the dose to the one that best suits the patient. In this way, we avoid deterioration of heart function and excessive hypotension.

If we need to discontinue the use of these drugs, this is also done gradually, i.e., we reduce the dose slowly over several weeks until complete discontinuation. Otherwise, the underlying disease that we treated may worsen.

In a word: start slow and stop slow!

CARDIOTONIC GLYCOSIDES

Cardiotonic glycosides are named after their two-part molecule, one part of which (genin) increases the force of cardiac contraction ("tones" the heart), and the other ensures the drug's solubility in water and movement through the body (a chain of sugars, i.e., the glycosidic part). The most important representative of this group of drugs is digoxin. Cardiotonics block Na+, K+, ATP-ase in the heart cell membrane, causing depolarization, then Ca++ channels open. The Ca++ ion enters the cells, binds to troponin and increases the force of myocardial contraction. Because of this effect, cardiotonics are still used for the treatment of heart failure, but only when the symptoms cannot be controlled with other drugs (ACE-inhibitors and beta-blockers are at the forefront in the treatment of heart failure today, as they have been shown to reduce the mortality of these patients for even 30%). In addition, they stimulate parasympathetic fibers in the heart and lead to the release of acetylcholine, which then slows conduction through the A-V node via muscarinic receptors. This reduces the number of impulses that pass from the atria to the ventricles. We use this cardiotonic action to treat atrial fibrillation to reduce the number of impulses that activate the ventricles.

Cardiotonics can easily be overdosed because they have a narrow therapeutic range. Their unwanted effects are manifested on the heart and outside the heart. Cardiac side effects are ventricular arrhythmias, initially extrasystoles of the bigeminy type (one normal, then one abnormal beat), which can later progress to ventricular tachycardia and fibrillation. Extracardiac side effects of cardiotonics are nausea and vomiting, seeing a yellow halo around objects and psychosis. The toxicity of cardiotonics increases if the patient has

hypokalemia, so it must be corrected in people receiving cardiotonics. An overdose of cardiotonics can be successfully treated with an antidote, Fab fragments of antibodies that bind to cardiotonics and prevent their effect on tissues.

TREATMENT OF HEART FAILURE

As already mentioned, today the drugs of choice for the treatment of heart failure are drugs from the group of ACE-inhibitors and beta-blockers. These two groups of drugs not only alleviate the symptoms of heart failure, but also reduce mortality. Today, we use cardiotonic glycosides only for the treatment of heart failure accompanied by severe symptoms and atrial fibrillation. Cardiotonics reduce the symptoms of heart failure, but not mortality.

ANTIARRHYTHMICS

Antiarrhythmic drugs are drugs used to prevent the occurrence of more serious heart rhythm disorders (tachycardia, flutter and fibrillation) or to interrupt already occurring disorders. Antiarrhythmics are not used to treat ordinary extrasystoles. They are divided into 4 groups: I group - antiarrhythmics that block ion channels for Na+; the main representatives are procainamide and quinidine (Ia group), lidocaine (Ib group) and propafenone (Ic group); II group - beta-blockers that, due to the blockade of β1 receptors in the heart, reduce the influence of sympathetic nerves on the heart; in this group, propranolol is mostly used as an antiarrhythmic; III group - drugs that block ion channels for K+, and representatives of this group are sotalol and bretylium; IV group - antiarrhythmics that block channels for Ca++, the main representative is verapamil.

A special antiarrhythmic drug that works by almost all of the previously mentioned mechanisms is amiodarone.

A side effect of many antiarrhythmic drugs is weakening of the heart, and all antiarrhythmic drugs can cause arrhythmias themselves, especially if they are taken in higher doses. The first sign that an antiarrhythmic drug can cause a serious ventricular arrhythmia is a change in the length of the interval between the Q wave and the end of the T wave in the electrocardiogram (ECG): if this interval becomes longer than 460 milliseconds with a normal heart rhythm, the patient is at high risk of serious ventricular arrhythmia, so

the dose of antiarrhythmics that the patient is already receiving should be urgently corrected.

Antiarrhythmics can only be introduced into therapy by a cardiologist and that in hospital conditions. The use of antiarrhythmic drugs must not be stopped suddenly, because arrhythmias can occur when stopped suddenly. The most important use of antiarrhythmics today is related to the treatment of ventricular arrhythmias after myocardial infarction. Amiodarone is mostly used for this purpose today. Although it is a very effective drug, amiodarone has very pronounced side effects if used for a long time: pulmonary fibrosis, damage to the thyroid gland, clouding of the cornea, grayish discoloration of the skin, and hair loss. Only slightly higher daily doses of amiodarone than recommended are toxic to the liver, causing chemical hepatitis. That's why we try to use amiodarone as short as possible, and in as small, yet effective, doses as possible.

DRUGS AGAINST HYPERLIPIDEMIA

Serum cholesterol level should be below 5 mmol/l and triglyceride level below 2 mmol/l. If these values are higher, the patient would have to follow a diet low in fat and low in simple carbohydrates. If after three months the diet has not normalized the level of cholesterol and triglycerides, drugs should be used to lower blood fats. The patient must take these medicines for life and at the same time follow a diet.

To lower cholesterol levels, we primarily use drugs from the **statin group**, which work by reducing cholesterol synthesis in the liver. The representative of this group is atorvastatin. A problem with the use of these drugs is possible damage to the liver and/or striated muscles. That is why we must periodically measure the level of transaminases in the patient's plasma and warn him/her to immediately stop taking the medicine if he/she feels muscle pain. When muscle pain occurs, the level of creatine kinase in the plasma, an enzyme that is a marker of damage to the cells of the striated muscles, should be measured.

Recently, a monoclonal antibody has come into use against a specific protein from the blood, which normally reduces the number of receptors for LDL-lipoproteins (cholesterol-rich blood lipoproteins) on liver cells. The name of that monoclonal antibody is **evolocumab**. Subcutaneous administration of evolocumab every 2 weeks results in an increase in the number of receptors for LDL-lipoproteins on liver cells, which then rapidly take up these cholesterol-rich lipoproteins, which results in a large drop in blood cholesterol levels (up to 75% compared to initial values). Evolocumab is currently the most effective blood cholesterol lowering drug available.

We reduce the level of triglycerides with drugs from the **fibrate** group, which increase the breakdown of chylomicrons and VLDL (Very Low Density Lipoproteins) particles in peripheral tissues. A representative is the drug **bezafibrate**. Similar to statins, fibrates can damage the liver and muscles, and can lead to the formation of gallstones.

PHARMACOLOGY OF HORMONES

HORMONES OF THE HYPOTHALAMUS AND PITUITARY

Peptide hormones are secreted in the hypothalamus and reach the anterior lobe of the pituitary gland directly through the local circulation, where they control the release of other hormones. Gonadorelin (gonadotropin releasing hormone - GRH) is a natural hypothalamic hormone that controls the release of gonadotropin hormones in the pituitary gland. In small doses, and when used intermittently (pulsely), gonadorelin stimulates the release of gonadotropic hormones FSH (follicle-stimulating hormone) and LH (luteinizing hormone), while in the case of continuous use, it leads to the cessation of secretion of these hormones in the pituitary gland. Several analogues of gonadorelin have been synthesized, which are administered as depot preparations intramuscularly or subcutaneously (triptorelin, goserelin), so that due to their continuous presence in the blood, they lead to the blockade of the release of gonadotropins (FSH and LH). Gonadorelin analogues are used in the treatment of hormone-dependent tumors (e.g., prostate cancer), endometriosis and premature puberty, because by blocking the release of gonadotropins, they prevent the synthesis of sex hormones in the ovaries in women and testicles in men, and thus their impact on target tissues.

Gonadotropins FSH and LH are used in the treatment of male and female infertility. In women, ovulation is induced by these hormones, and in men spermatogenesis is enhanced. In the past, these hormones were obtained from the urine of pregnant women (there is human chorionic gonadotropin, which acts as a luteinizing hormone) and menopausal women (there is human menopausal gonadotropin, which is actually a natural follicle-stimulating hormone). Today, follicle-stimulating and luteinizing hormone preparations are used, which are produced by recombinant technology, by introducing and activating a specific gene in cell lines. They are applied subcutaneously, with an interval of several days, until ovulation is achieved in women, and the number of functional spermatozoa increases in men. The most important side effect of gonadotropins is the occurrence of ovarian hyperstimulation syndrome, when the patient feels pain in the abdomen, and when fluid accumulates in the abdominal and chest cavity. If not treated

appropriately (discontinuation of gonadotropins, balanced fluid intake), ovarian hyperstimulation syndrome can be complicated by kidney failure or phlebotrombosis.

Somatotropic hormone (STH – growth hormone) is compensated for in children who do not produce it in the normal amount in the pituitary gland, and as a result they lag behind in growth. Today, only growth hormone preparations obtained by recombinant technology are used for compensation. Side effects of somatotropic hormone can include swelling of the extremities with or without carpal tunnel syndrome, gynecomastia in men and back pain. In the event that the somatotropic hormone is secreted more than necessary, i.e., uncontrolled (e.g., when there is a pituitary tumor, so gigantism occurs in children, and acromegaly in adults), its secretion can be reduced by the use of analogues of the hypothalamic hormone somatostatin, which will inhibit tumor cells and lead to their accelerated deterioration. Somatostatin analogues are octreotide (octapeptide) and lanreotide (cyclic octapeptide) which are given intramuscularly once a month. Another way to suppress the excessive effect of growth hormone on target tissues is the administration of pegvisomant, a growth hormone receptor blocker; pegvisomant is also proteinaceous in nature, and is given as a subcutaneous injection.

If a person has a tumor of the pituitary gland that secretes prolactin, if it is female, it will cause amenorrhea and galactorrhea, and if it is male, it will cause gynecomastia and even galactorrhea, with a decrease in testosterone synthesis. The growth of prolactin-secreting tumors can be stopped and the serum prolactin level normalized if dopamine receptor agonists are used: bromocriptine, cabergoline and quinagolide. These drugs are administered orally and are very effective, but in a small number of patients they cause retroperitoneal fibrosis and/or endocardial fibrosis leading to valvular insufficiency in the heart.

Peptide hormones oxytocin and vasopressin are secreted in the posterior lobe of the pituitary gland. We use oxytocin for the induction and stimulation of childbirth in the form of intravenous infusion, and also to promote milk secretion in the form of a nasal spray. Vasopressin (antidiuretic hormone - ADH) is used to treat diabetes insipidus (increased urine output due to lack of antidiuretic hormone) and to reduce bleeding from esophageal varices. A long-acting analog of vasopressin is called terlipressin. Both vasopressin and terlipressin can lead to myocardial ischemia, arrhythmias, and increased blood pressure.

In the event that vasopressin is secreted more than it should be, so the excretion of water in the kidneys is reduced, hyponatremia can occur. Hyponatremia of this type can be treated with an antidiuretic hormone receptor blocker, tolvaptan, which is administered orally. An oxytocin receptor blocker is called atosiban. It is used as a tocolytic, i.e. to prevent premature birth and miscarriage in late pregnancy because it reduces uterine contractions.

INSULIN

Insulin is a hormone that allows glucose to enter cells, and its participation in intracellular metabolism. We use insulin to treat type 1 diabetes, gestational diabetes, and some patients with type 2 diabetes whose disease control can no longer be achieved with oral antidiabetics. Also, when patients with type 2 diabetes who take oral antidiabetic drugs undergo surgery, they must switch to insulin before, during and after surgery. The first preparation of insulin entered clinical use in 1923, and had to be administered several times a day in the form of injections.

Today, insulin preparations are divided into short-acting, medium-acting and long-acting. **Short-acting** insulin is also called crystalline insulin. It is the only one that can be given both subcutaneously and intravenously. It starts working after half an hour and works for about 6 hours. **Intermediate-acting insulins** are insulin-lente (obtained by changing the size of insulin crystals) and isophane-insulin (obtained by mixing insulin with protamine). They are applied only subcutaneously and begin to work after 2 hours, and their effect lasts 24 hours. **Long-acting insulins** are insulin-ultralent (with even larger crystals than insulin lente) and protamine-zinc-insulin (with a higher content of protamine than isophane insulin). They are given only subcutaneously. They begin to work after about 3 hours, and their effect lasts up to 36 hours. There is a large number of insulins from different manufacturers and under different names on the market, but all of them can be classified into one of the mentioned types of insulin. In the past, these insulin preparations were made from insulin of animal origin, however, due to their high immunogenicity, today only human insulins, obtained by recombinant technology from cell lines, are produced and used.

Classical insulin therapy is such that the patient receives one daily dose of medium-long-acting insulin in the morning (so-called "basal" insulin), and then half an hour before breakfast, lunch and dinner, one additional dose of crystalline insulin (so-called "bolus" insulin). We monitor the effect of insulin through the level of glycemia or through the percentage of glycosylated hemoglobin, which should be less than 7.5%. The level of glycosylated hemoglobin is measured every 3 months.

In addition to natural insulin preparations, there are also **insulin analogues**, i.e. drugs that differ from insulin in that some of the amino acids have been replaced in the peptide chain. They are more expensive than regular insulin because they are more comfortable to use. One part of the analogues belongs to the so-called **ultra-short-acting preparations**, such as insulin-aspart, insulin lispro and insulin glulisine. These drugs, like crystalline insulin, are given before each meal, but the patient can eat immediately after

their administration (they can even be administered during a meal), while after administering crystalline insulin, he must wait exactly half an hour. There are also **long-acting insulin analogues**, e.g. insulin glargine, insulin degludec or insulin detemir. Compared to classic long-acting insulin, these analogues are characterized by a more gradual onset of action, a stable level in the blood without "jumps" and an even longer effect.

In practice, insulin **"premixes"** are sometimes used, i.e. combined preparations containing intermediate/long-acting and short-acting insulin or analogs in the same injection. Although they are administered in fewer injections per day (one to two), which may be attractive to patients, they do not achieve as good glycemic control as when basal and bolus insulins are administered separately.

Insulins are classically prepared in a concentration of 100 units per 10 ml. Recently, however, concentrated insulin preparations have been made, up to 500 units per 10 ml, which are used in patients whose insulin needs are extremely high. There is also a preparation of short-acting insulin that is administered by inhalation, so patients can use it instead of "bolus" insulin injections before meals. This inhaled insulin can cause bronchospasm in some patients, so spirometry monitoring is necessary every 6 months.

The main side effects of insulin are hypoglycemia and atrophy of the subcutaneous tissue at the site of administration.

ORAL ANTIDIABETIC DRUGS

Oral antidiabetic drugs are drugs that represent an alternative to insulin in the treatment of diabetes type 2. Although they can successfully control the level of glycemia in the blood, they have not yet been proven to prevent the frequency of diabetes complications, which is normally achieved by the disciplined use of adequate doses of insulin. There are several groups of oral antidiabetics, but therapy is always started first with a drug from the biguanide group - metformin. Only if the control of glycemia and glycosylated hemoglobin was not achieved with metformin, drugs from other groups are added to it, so the patient is usually treated with a combination of oral antidiabetic drugs. Insulin is included in the treatment of type 2 diabetes when oral antidiabetics cannot control the disease sufficiently, as well as during surgical treatment in the hospital or treatment of severe infections.

Sulfonylurea derivatives - representative of this group is glipizide. The mechanism of action of sulfonylurea derivatives is the closing of K+ channels in the membrane of pancreatic beta cells, which causes depolarization and release of insulin. The most important

side effects of these drugs are: hypoglycemia, increased appetite and hyponatremia. Because of their long-term effect, hypoglycemia is particularly common in patients with renal insufficiency and in elderly patients.

Meglitinides – representative is repaglinide. These drugs also release insulin from the pancreas, but unlike drugs from the previous group, they work for a short time, only two hours. The main side effects of meglitinide are hypoglycemia and an increased incidence of acute coronary syndrome.

Biguanides - the main representative of this group is metformin. Today, the treatment of type 2 diabetes is almost always started with metformin. Medicines from this group promote the entry of glucose into peripheral tissues. The good sides of these drugs are that they reduce appetite and rarely cause hypoglycemia. On the other hand, metformin can lead to deterioration of kidney function, especially in circumstances where the patient is dehydrated or his circulation through the kidneys is compromised. That is why metformin administration is stopped two days before and two days after major surgical procedures, as well as during X-ray imaging where iodine contrast agents are used. A patient on metformin therapy should periodically monitor kidney function - if creatinine clearance falls below 30 ml/min, metformin must not be used. Finally, biguanides can cause lactic acidosis in the patient, so it should be considered if the patient complains of abdominal pain, muscle spasms, weakness and difficulty breathing.

Thiazolidinediones - representatives are pioglitazone and rosiglitazone. These drugs promote the use of glucose in peripheral tissues, because they mimic the action of insulin. They can cause hypoglycemia, but they also retain fluid in the body, so the condition can worsen in patients with heart failure. Rosiglitazone sometimes causes myocardial ischemia. Pioglitazone increases the risk of bladder cancer, as well as foot or hand bone fractures in women with osteoporosis. Due to the listed side effects, drugs from this group are used extremely rarely or not at all.

Medicines that act through incretins. Incretins (glucagon-like polypeptide 1 and glucose-dependent insulinotropic peptide) are peptide hormones secreted in the mucosa of the small intestine after a meal, and increase insulin release, decrease glucagon release, and slow gastric emptying. All the mentioned effects contribute to the slow absorption of glucose and the lowering of glycemia. Their analogues have been created, the most famous of which are exenatide and liraglutide. Exenatide and liraglutide are given as subcutaneous injections. Another way to enhance the effect of incretins is to block their breakdown, which is achieved with drugs from the gliptin group (e.g., sitagliptin), which are administered orally and block the dipeptidyl-peptidase 4 enzyme, which normally breaks down incretins. Incretin analogues can worsen kidney function and cause pancreatitis or gastric paresis. The main side effects of gliptins are an increased risk of pancreatitis and hypoglycemia. The

good side of incretin analogues is in reducing the mortality of patients who receive them, which is especially proven for liraglutide.

Glucose transporter blockers in renal tubular cells. Dapagliflozin and empagliflozin are drugs from this group that block the transporter for glucose in the cells of the proximal tubules (it is actually a co-transporter of glucose and sodium type 2, whose transport capacity is large), as a result of which the reabsorption of glucose is prevented and its excretion in the urine is increased. These drugs are used as additional therapy for type 2 diabetes, in addition to the existing drugs that the patient is taking. Dapagliflozin and similar drugs cannot be prescribed to patients with weakened kidney function, and should also be avoided in people who are in a state of dehydration; there has also been an increase in the number of cases of diabetic ketoacidosis with these drugs compared to other oral antidiabetics. On the other hand, empagliflozin has been shown to reduce mortality in people with diabetes or heart failure, which is an additional reason for using these drugs.

A special oral antidiabetic drug is **acarbose**. It works by inhibiting the breakdown of sucrose in the intestinal lumen, so glucose is more difficult to absorb. It is used only as an additional medicine.

GLUCAGON

Glucagon is a hormone secreted by the alpha-cells of the endocrine pancreas, whose role is reduced to the stimulation of glycogenolysis and the release of glucose from the liver, which causes hyperglycemia. It also relaxes the smooth muscles of the gastrointestinal tract, accelerates the heartbeat and increases the force of heart contraction. Glucagon is used as a 1 mg injection to treat hypoglycemic coma, acute heart failure (although recent studies have not proven its effectiveness), and bradycardia in beta-blocker overdose.

THYROXINE AND ANTITHYROID DRUGS

Thyroxine (tetra-iodo-thyronine) is a thyroid hormone used orally to treat hypothyroidism and goiter. In peripheral tissues, thyroxine is converted to triiodothyronine, which is the active form, and which causes effects in the tissues.

In the event that thyroxine is excessively secreted (hyperthyroidism), we use drugs that inhibit the incorporation of iodine into tyrosine, thus reducing the secretion of

thyroxine. Representatives of this group are **methimazole and propylthiouracil**. When using these two drugs, the general practitioner and the dentist should watch out for the appearance of fever and sore throat in the patient. Sore throat and fever can occur due to agranulocytosis (a decrease in the number of neutrophil granulocytes), which is sometimes caused by methimazole and propylthiouracil. When this happens, the patient should be urgently sent to the hospital for intensive antibiotic therapy and further administration of the drug should be discontinued.

Hyperthyroidism can also be treated with a single use of radioactive iodine, which completely destroys the thyroid gland. After such therapy, the patient must take thyroid hormone replacement for life, i.e. thyroxine, orally.

CORTICOSTEROIDS

By corticosteroids we mean hormones that are secreted from the cortex of the adrenal gland (aldosterone, glucocorticoids, androgens). Of the corticosteroids, the most clinically used are glucocorticoids, which are secreted from the cells of the middle zone of the cortex (zone fasciculata); to the greatest extent, cortisol is secreted from glucocorticoids, which when prepared as a medicine is called hydrocortisone. Cortisol has a large number of effects in the body, most of which are used in practice for anti-edematous, anti-inflammatory, immunosuppressive, anti-allergic and anti-tumor effects. In addition to hydrocortisone, there are several synthetic glucocorticoids, of which we use the most: dexamethasone (for the treatment of edema in general, especially brain edema, given both orally and parenterally), methylprednisolone (for the treatment of severe allergic reactions, severe asthma attacks and inflammatory diseases; given parenteral) and prednisone (used orally). Corticosteroids bind to intracellular receptors and regulate protein expression.

Because of these effects, corticosteroids are used to treat edema, various inflammations (including autoimmune diseases), to treat anaphylactic reactions, to prevent transplant rejection, and to treat leukemias and lymphomas. Postoperative use of dexamethasone is particularly important in dentistry, which reduces swelling due to tissue bruising and thus accelerates recovery (a single dose is administered intramuscularly immediately after surgery). Dexamethasone also prevents postoperative vomiting. Glucocorticoids are also widely used in the form of inhalation, for the prevention and treatment of bronchial asthma attacks (e.g., beclomethasone, fluticasone, etc.).

If glucocorticoids are given for up to 7 days, they practically have no side effects, and if they are given longer, they cause Cushing's syndrome, hypertension, osteoporosis, stress ulcers, cataracts, skin atrophy with pustular measles, and adrenal atrophy. After

prolonged use, they must not be stopped suddenly, because acute adrenal insufficiency may occur.

USE OF CORTICOSTEROIDS IN DISEASES OF THE TEETH AND ORAL CAVITY

Corticosteroids are used in a large number of dental and oral cavity diseases, primarily due to their anti-inflammatory and anti-edematous effect.

Aphthous stomatitis. Aphthous stomatitis is an inflammation of the mucous membrane of the oral cavity with the appearance of painful ulcers (ulcers) covered with a white layer of fibrin. Since aphthous stomatitis is the result of inflammation without infection, the use of corticosteroids due to their anti-inflammatory effect leads to rapid healing. Most often, corticosteroids are applied locally to the sores themselves, in the form of a gel containing fluocinonide, triamcinolone or clobetasol. The gel is applied between meals, 2 to 3 times a day.

Application after dento-alveolar operations. Any operation in the oral cavity is accompanied by swelling and transudation of liquid through the openings on the mucous membrane. In order to reduce swelling and transudation, after surgery, patients are immediately given some of the corticosteroids parenterally, in the form of an intramuscular injection. Most often, dexamethasone is used, but in its absence, methylprednisolone can also be used. This application of corticosteroids is very effective, and without significant side effects.

Mucoceles. Mucoceles are cysts that arise under the mucous membrane in the oral cavity, mostly on the palate. They can be successfully treated with corticosteroid injections.

Endodontic pain. After instrumental or chemical treatment of root canals, patients suffer of extremely severe pain due to inflammation. If, during root canal intervention, a small amount of triamcinolone acetonide is injected into the root canal itself, it will reduce inflammation and prevent severe pain after the intervention.

Arthritis of the temporomandibular joint. Inflammation of the joint that connects the lower jaw to the temporal bone can occur as part of a systemic inflammatory disease (e.g., rheumatoid arthritis) or as a result of degenerative damage to the cartilage of the joint. Patients then have problems with chewing, which is painful. Corticosteroids can then be injected directly into the joint; after one injection, the beneficial effects last up to a year. Betamethasone acetate, triamcinolone acetonide or methylprednisolone acetate are most commonly injected.

Bullous pemphigoid. Bullous pemphigoid is an autoimmune disease in which huge blisters (bullae) appear in the oral cavity. These blisters burst and put on a sore and painful surface. Bullous pemphigoid can be successfully treated with systemic or local corticosteroids.

ESTROGENS AND GESTAGENS

Female sex hormones, estrogens, normally exist in three forms: estradiol, which is created in the ovaries, estrone, which is produced by metabolizing estradiol, but also by transforming the androgen androstenedione in adipose tissue (which is why it is the main estrogen in menopause), and estriol, which is most present in pregnancy, because it is created in the placenta. If pure estrogens are administered orally, they are rapidly metabolized in the liver, and a small percentage reaches the systemic circulation. That is why sulfate esters of estrone are used for oral use, which we call conjugated estrogens, and which can be administered orally with satisfactory bioavailability. Synthetic estrogens, e.g., ethinyl estradiol or mestranol are also more resistant to degradation in the liver, so they can be administered orally.

Estrogens are used for contraception, to replace hormones in menopause and to stop menorrhagia (dysfunctional uterine bleeding that continues with normal menstruation). In the first two indications, estrogens must be combined with progestogens in women who have a uterus (that is, it has not been removed by surgery), because this reduces the risk of endometrial cancer. The most serious side effect of estrogen is a greater tendency to develop venous thromboses. In addition, they lead to hypertension and increase the incidence of breast and endometrial cancer.

Selective estrogen receptor modulators (tamoxifen and raloxifene) block estrogen receptors in some tissues and stimulate them in others, while in others they have no effect at all. Thus, tamoxifen blocks estrogen receptors in breast tumors, so they are used to treat breast tumors that are sensitive to estrogen. Raloxifene stimulates estrogen receptors in bones, so it is used to treat postmenopausal osteoporosis.

The natural progestogen is progesterone, which is produced in the corpus luteum after ovulation, in the placenta and in the adrenal cortex. Due to rapid breakdown in the liver, progesterone can only be administered parenterally, in the form of depot injections. Synthetic progestogens (norethindrone, levonorgestrel, desogestrel, etc.), which also activate progesterone receptors, are more resistant to degradation in the liver, so they can be administered orally. Progestogens are used in combination with estrogens as oral contraceptives, and for hormone replacement in menopause. Adverse effects of progestogens are headache, depression, acne, hirsutism and weight gain.

ANDROGENS

Of the androgens, the drug used is testosterone, which is administered as a depot intramuscular injection. Testosterone is used in men with hypogonadism. In addition to testosterone, anabolic steroids are used, which have a weaker masculinizing effect than testosterone, but increase the volume and strength of muscles because they promote the incorporation of amino acids. We use anabolic steroids to treat cachexia (e.g., in hemodialysis patients or those being treated for HIV infection) - an example is the anabolic steroid nandrolone, which is administered as a depot preparation, nandrolone-decanoate, for two weeks, in the form of an intramuscular injection. injections.

A testosterone receptor blocker is the drug flutamide. It is used to treat testosterone-dependent prostate cancer.

TREATMENT OF BENIGN PROSTATE HYPERPLASIA

Benign prostate enlargement is common in men over the age of 50. It is treated with the use of **finasteride or dutasteride**, drugs that block the enzyme 5-alpha-reductase and the conversion of testosterone into the active form of dihydrotestosterone. These drugs are applied for 6 months and the prostate gradually shrinks. The main side effects of finasteride and dutasteride are impotence and a decrease in sperm quality. In addition to the 5-alpha-reductase blocker, patients with benign prostatic hypertrophy also take an alpha-blocker (eg tamsulosin), which relaxes the sphincter in the neck of the bladder and thus additionally facilitates urination. Therapy with a combination of 5-alpha-reductase blockers and alpha-1 blockers is more effective than therapy with each of these drugs separately.

TREATMENT OF OSTEOPOROSIS

All patients who have osteoporosis (whose bone density is less than normal, i.e., T-score less than -2.5) should take vitamin D in a dose of about 400 units and calcium carbonate in a dose of 1.5 grams daily. However, just using vitamin D and calcium is not enough, because osteoporosis will still progress. The drugs of first choice for osteoporosis are bisphosphonates, which prevent bone breakdown, because they inhibit the function of

ostoclasts. Representatives of this group are alendronate and ibendronate, which are taken orally, and pamidronate, which is administered as an i.v. injection. If they are not taken with enough water and remain in the lower third of the esophagus, oral bisphosphonates can cause severe esophagitis with ulceration. On the other hand, parenterally administered bisphosphonates tend to damage kidney function, especially in people who already have kidney failure.

A number of patients taking bisphosphonates will not respond favorably to these drugs, ie. osteoporosis will continue to progress. In such a situation, we replace bisphosphonates with denosumab (a monoclonal antibody against a blood protein that activates osteoclasts), or teriparatide (a synthetic parathormone with 34 amino acids that activates osteoblasts due to intermittent administration). Both mentioned drugs are administered as a subcutaneous injection (denosumab once every 6 months, and teriparatide daily). Denosumab increases the tendency to develop skin infections (e.g. herpes), and teriparatide increases the level of cholesterol in the blood, causes depression and neuralgic pains.

PHARMACOLOGY OF BLOOD AND TISSUES

ORAL ANTICOAGULANT DRUGS

Classic oral anticoagulant drugs interfere with the reduction of vitamin K in the liver, which reduces the concentration of coagulation factors in the blood. The most important drug from that group is **warfarin**. Once warfarin is started, it takes one to three days to reduce blood coagulability sufficiently. The effect of warfarin is measured by the INR ratio (the ratio of the patient's prothrombin time to the control's prothrombin time), which should be between 2 and 3. Classic oral anticoagulants are used to treat deep vein thrombosis and pulmonary embolism, as well as to prevent embolism in patients with atrial fibrillation. They are also prescribed for life for a patient who has artificial valves. If oral anticoagulants are overdosed, their effect can be stopped immediately by the administration of fresh frozen plasma (containing coagulation factors), and with a delay of 12 to 24 hours by the administration of vitamin K. The most serious side effect of warfarin is bleeding in the brain or gastrointestinal tract, which occurs if its effect on coagulation is enhanced due to overdose or interactions with other drugs or food.

In an effort to overcome the unsafe dosing of warfarin, the so-called "new" oral anticoagulant drugs, which act either by direct inhibition of thrombin (**dabigatran**), or by

direct inhibition of activated coagulation factor Xa (**rivaroxaban, apixaban**). New oral anticoagulant drugs are also used to treat deep vein thrombosis and prevent embolism in atrial fibrillation, but unlike warfarin, they do not require monitoring of the effect with a test similar to the INR-test. Unlike warfarin, these drugs interact less with other drugs or food, but serious bleeding in the brain or gastrointestinal tract is almost as common with them as with warfarin.

HEPARIN

Heparin is a mixture of complex carbohydrates obtained from the mucous membrane of the digestive tract of domestic animals. Heparin binds to antithrombin 3 and together with it inhibits thrombin (coagulation factor 2). Heparin is administered intravenously and subcutaneously. It starts working immediately. It is used for the prevention of deep vein thrombosis during surgical interventions or long-term lying down, as well as for the treatment of deep vein thrombosis and pulmonary embolism. The anticoagulant effect of heparin is measured by activated partial thromboplastin time (aPTT), which should be about 2 times longer than without heparin administration.

The application of heparin should not be long-term, because after a week of application there is a possibility of thrombocytopenia, that could be accompanied by thrombosis in the arteries of the extremities, which is manifested by gangrene of the fingertips. If such "heparin-induced thrombocytopenia" occurs, heparin is stopped immediately, and direct thrombin inhibitors should be administered parenterally, such as **bivalirudin and argatroban**, to prevent further thromboses. In order to avoid the possibility of thrombocytopenia, the use of heparin is already replaced after 5-7 days by the use of oral anticoagulants (2-3 days overlap the use in the case of warfarin, until it starts to work).

LOW MOLECULAR HEPARINS

Low molecular weight heparins are obtained by purifying ordinary heparin, so the carbohydrate chains are much shorter, but they contain a sequence that is the carrier of the therapeutic effect. Low molecular weight heparins work by inhibiting coagulation factor 10, and are administered subcutaneously, usually in the area around the navel. They are used for the same indications as heparin, but their administration is easier, because it is not necessary to control aPTT. The most important representatives of low molecular weight heparins are

enoxaparin and dalteparin. Unfortunately, even low-molecular-weight heparins can cause "heparin-induced thrombocytopenia", so caution is needed when using them for a long time (e,g,, in pregnant women, or if the patient cannot take oral anticoagulants for some reason).

VITAMIN K

Vitamin K is necessary for the synthesis of coagulation factors. When there is not enough vitamin K, bleeding occurs in many tissues, and the most dangerous are bleeding in the brain and from the mucous membrane of the stomach or duodenum at the site of the ulcer. Vitamin K deficiency occurs in newborns (especially premature babies), because they do not yet have the bacteria in their intestines that normally produce vitamin K. Vitamin K deficiency also occurs in obstructive jaundice. Finally, we sometimes have to use vitamin K in case of warfarin overdose.

There are three forms of vitamin K, K1, K2 and K3, but the most commonly used is vitamin K1 or phytomenadione. Phytomenadione is administered intravenously or intramuscularly (in infants only). Intravenous administration must be very slow, because with rapid administration, histamine and other mediators are released from mast cells and basophils, resulting in a condition similar to an anaphylactic reaction, which is called an "anaphylactoid reaction" (the patient has hypotension, difficulty breathing due to swelling of the airways, can urticaria on the skin, etc.).

COAGULANT MEDICINES FOR LOCAL APPLICATION IN THE ORAL CAVITY

After difficult tooth extractions or extensive surgical interventions in the oral cavity, the operative site can bleed a lot. Bleeding can be stopped by applying to the site of intervention a resorptive coagulant agent: oxidized regenerated cellulose, gelatin sponge, collagen (synthetic or microcrystalline or porcine), n-butyl-2-cyano-acrylate glue or fibrin glue (consists mainly of thrombin and fibrinogen). Once one these hemostats is placed in the wound, it can be sutured with resorbable suture; the patient should then be given a roll of wet gauze to bite over it, and to press the gauze on the wound - after about 10 minutes of pressure, the bleeding usually stops.

Oxidized cellulose is obtained by exposing ordinary cellulose to an oxidizing agent (e.g., hydrogen peroxide). The oxidizing agent leads to the formation of aldehyde and keto groups in cellulose, so that it more easily activates the blood coagulation system.

After surgery or tooth extraction, when hemostasis is established, the process of fibrinolysis is activated. Fibrinolysis erodes coagulum, and after a few days can cause subsequent bleeding. To prevent this, patients are given a mouth rinse after surgery with a solution containing antifibrinolytics (5% tranexamic acid, 4 times a day, 7 days, or 25% epsilon-aminocaproic acid, 4 times a day, 7 days). Such local application of antifibrinolytics is very effective, as it reduces the frequency of postoperative bleeding from 40% to only 7%.

IRON

Due to the lack of iron in the diet or chronic blood loss, hypochromic anemia occurs, in which the number of erythrocytes is not greatly reduced, but the amount of hemoglobin in them is greatly reduced. Then the patient should be compensated with iron. If we know that there are 470 mg of iron in one liter of blood and if we know the hemoglobin level in the patient's blood, we can calculate the amount of iron that should be given to the patient. We calculate it as follows - we divide the difference between the hemoglobin concentration of a healthy person and the hemoglobin concentration of our patient by the hemoglobin concentration of a healthy person. We multiply the number obtained (it must be less than 1) by 470 milligrams and by the number 5 (this is due to 5 liters of blood), which gives us the amount of iron that is missing in the blood. We add another 500 mg to this amount, which is the amount of iron normally found in the liver of a healthy person. We can give the amount of iron calculated in this way to the patient intravenously in the form of only one injection (preparation Fe-dextran or Fe-gluconate). If we want to compensate the patient with iron orally, we give Fe-sulfate, but in an amount that is 10 times higher than the calculated amount, because only 10% of the ingested amount of iron is absorbed from the digestive tract.

When taken orally, iron regularly causes nausea and loss of appetite, because it irritates the mucous membrane of the stomach. Also, after oral administration of iron, the stool becomes black, so the patient should be warned about this. On the other hand, parenteral administration of iron is sometimes accompanied by an anaphylactoid reaction.

VITAMIN B12 AND FOLIC ACID

If the body lacks vitamin B12 and/or folic acid, megaloblastic anemia occurs. Vitamin B12 deficiency also causes damage to the nerve pathways in the back columns of the spinal cord, which is manifested by the loss of proprioception (feeling of the position of the limb), and is called funicular myelosis. Both vitamins are necessary in the methylation processes of nucleic bases. If the patient has megaloblastic anemia, since we do not know whether it is a deficiency of both or just one vitamin, we must compensate for both vitamin B12 and folic acid.

Vitamin B12 is administered as an intramuscular injection of 2.5 mg once a month. Folic acid is administered orally in the form of one 5 mg tablet per day. In addition, folic acid should be given in a dose of 0.4 to 1 mg per day to all pregnant women in the first half of pregnancy because it prevents neural tube anomalies.

ANTIAGGREGATION DRUGS

Antiplatelet drugs prevent the formation of thrombus in arteries, primarily coronary and brain arteries. That's why these drugs are given to people who are at risk of myocardial and brain infarction, in order to prevent these conditions, and they are especially effective if the patient already had problems with atherosclerosis, i.e,. has symptomatic coronary disease or has already suffered a stroke. In such situations, for the prevention of arterial thrombosis, patients are given one of the anti-aggregation drugs, which they take permanently.

Special attention is paid to patients who, due to coronary disease, have a stent implanted in their coronary arteries, i.e.,. a metal tube that maintains the patency of the blood vessel. Such patients must take dual antiplatelet therapy from the moment the stent is implanted for the next year, because they are at increased risk for thrombosis and stent blockage.

The first antiplatelet drug was aspirin in smaller doses (up to 100 mg per day), because it interferes with the synthesis of thromboxane in platelets and thus reduces platelet aggregation. After aspirin, several drugs were developed that block purinergic receptors of the $P2Y_{12}$ type, which are normally acted upon by the endogenous substances adenosine, adenosine-di- and -tri-phosphate, activating platelets. The first of this group was clopidogrel, whose main drawback is that it is not active on its own, but must be transformed in the liver to an active metabolite in order to work, whereby the active

metabolite inhibits the purinergic receptor irreversibly. In a number of people, these enzymes are less active, so clopidogrel was not effective, and numerous interactions with other drugs that block the metabolism of clopidogrel are possible. The irreversibility of the clopidogrel effect can also be a problem if the patient has to undergo a sudden surgical intervention, as he will be at a higher risk of bleeding. Clopidogrel was then replaced by ticagrelor and prasugrel, drugs that reversibly block the same purinergic receptors ($P2Y_{12}$), of which ticagrelor does not require prior activation through metabolism, i.e., it is directly active, so its effect is far more reliable than the effect of clopidogrel.

INTERACTIONS OF ANTIAGGREGATION DRUGS WITH OTHER DRUGS USED IN DENTISTRY

Although a large number of described interactions of antiaggregation drugs with other drugs can be found in the literature, only a small number of interactions have clinical significance, i.e., affects the further treatment of the patient or worsens his health condition. Aspirin interacts with oral anticoagulants or heparin, leading to further weakening of blood clotting, so patients may experience severe bleeding from the oral cavity, often after some intervention. To prevent this from happening, simultaneous use of aspirin with oral coagulants or heparin should be avoided. Also, if aspirin is used together with antidepressants and serotonin reuptake blockers, its antiaggregation effect and bleeding are enhanced. The use of aspirin should also be avoided in patients who are already using non-steroidal anti-inflammatory drugs (mainly for their analgesic effect), because then the unwanted effects of aspirin increase, especially on the gastrointestinal tract.

Similar to aspirin, clopidogrel, due to its antiaggregation effect, interacts with oral anticoagulant drugs or heparin, leading to further weakening of blood clotting, so that bleeding may occur after some intervention in the oral cavity. A whole series of drugs affects the antiplatelet effect of clopidogrel, mainly due to interference with its metabolism: carbamazepine, ciprofloxacin, erythromycin, esomeprazole and omeprazole, fluconazole, fluoxetine and fluvoxamine. Except for carbamazepine, which increases the effect of clopidogrel due to accelerated metabolism and creation of an active metabolite, other drugs inhibit the enzymes that metabolize clopidogrel and thereby hinder the creation of an active metabolite, which actually has an antiplatelet effect.

ADVERSE EFFECTS OF ANTIAGGREGATION MEDICINES IN THE ORAL CAVITY

The most significant side effects of anti-aggregation drugs in the oral cavity are:

• appearance of acute mucosal ulcerations

• bleeding after intervention

• bullous manifestations of Stevens-Johnson syndrome. Stevens-Johnson syndrome is characterized by the appearance of blisters on the skin and mucous membranes. This syndrome is caused by the activation of T-cytotoxic lymphocytes designated as CD8, which together with natural killer cells release granulysin and perforin, proteins that lead to keratinocyte (epidermal cell) apoptosis. Macrophages also release a ligand that binds to the Fas receptor on keratinocytes, activates it, and leads to keratinocyte apoptosis. Due to the death of keratinocytes, the epidermis separates from the dermis, interstitial fluid accumulates in that space and blisters form. The mortality of this syndrome is about 20%.

FIBRINOLYTICS

These drugs lead to the conversion of plasminogen into plasmin, a substance that breaks down the thrombus. Thrombolytics are given once intravenously to break up the thrombus in the coronary arteries in myocardial infarction, in the cerebral arteries in brain infarction, in the pulmonary arteries in pulmonary embolism (only in patients with extreme tachycardia and hypotension) and in deep veins in extremely large thromboses that spread. into the iliac veins and the inferior vena cava.

The most important fibrinolytics are streptokinase, which must be used only once (due to the possibility of a significant percentage of allergies), alteplase and tenecteplase, which can be used multiple times. Alteplase is actually a human enzyme, tissue plasminogen activator. Tenecteplase is somewhat modified alteplase, so that its effect lasts much longer than that of alteplase, and it has another advantage: it can be given as an intravenous injection, so in a shorter time than alteplase, which is given as an intravenous infusion. The biggest danger when using thrombolytics is bleeding.

SOLUTIONS FOR INTRAVENOUS ADMINISTRATION

We use crystalloid and colloidal solutions for fluid replacement. Of the crystalloid solutions, we use solutions that are isotonic with blood plasma (that is, they have 300 mOsmol/l). These are 5% glucose, 0.9% NaCl, Ringer's solution (which besides NaCl also

has Ca++ and K+) and Hartmann's solution (has the same composition as Ringer's plus lactate). If we give drugs in intravenous infusion, we can only use 5% glucose or 0.9% NaCl, and never Ringer's or Hartmann's solution, because in these two solutions there is a Ca++ ion that binds to the drugs and precipitates them.

Colloidal solutions are dextrans, gelatin solution and hydroxyethyl starch solution. Colloidal solutions, unlike crystalloid solutions, have a greater potential to retain fluid inside the blood vessels, because they do not pass completely through the walls of the capillaries into the perivascular tissue. We use colloid solutions very rarely in the most difficult patients in intensive care.

The standard 7.4% solution of KCl, which has 1 mmol K+ in 1 ml, is still important to us in practical medicine. This concentration was chosen for easier dosing, because by measuring the number of milliliters, we are actually counting the number of millimoles that should be applied. We use this solution for K+ replacement by adding a certain amount to the crystalloid solution before intravenous infusion (maximum 20 millimoles per 500 milliliter solution bottle). A solution of 8.4% NaHCO3 also has 1 mmol of bicarbonate in 1 ml. We use this solution intravenously to correct acidosis. Finally, hypocalcemia is treated with intravenous administration of Ca++- we give 10 ml of 10% Ca++-gluconate.

PHARMACOLOGY OF THE RESPIRATORY TRACT

TREATMENT OF BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE LUNG DISEASE

In the treatment of bronchial asthma, we have 2 key moments: prevention of attacks and cessation of asthma attacks. When it comes to chronic obstructive pulmonary disease, worsening (exacerbation) occurs due to infection and swelling of the respiratory mucosa, so similar drugs are used as in bronchial asthma.

For the prevention of asthma attacks or exacerbation of obstructive lung disease, we use drugs that can be administered by inhalation or orally. In the form of inhalation, we primarily use corticosteroids, which reduce inflammation in the airways and thus facilitate the passage of air. Fluticasone, beclomethasone and budesonide are the most commonly used inhaled corticosteroids today. Since they are administered by inhalation, only a small

amount of corticosteroids is absorbed into the blood, so side effects are not pronounced. The most common problem is the appearance of candidiasis in the oral cavity.

Very often, a fixed combination of corticosteroids and long-acting beta 2 agonists (salmeterol, formoterol, vilanterol, etc.) is used in the treatment of both asthma and chronic obstructive pulmonary disease. Corticosteroids reduce the swelling of the mucous membrane, and beta 2 agonists relax the smooth muscles and widen the airways. Sometimes a third drug is added to this dual therapy in the form of inhalation, a blocker of muscarinic receptors (ipratropium works for a short time, and tiotropium for a long time), which additionally relaxes smooth muscles and widens the airways.

A proportion of patients with bronchial asthma may also benefit from the oral leukotriene receptor blockers montelukast and zafirlukast. Since leukotrienes are inflammatory mediators and also have a bronchoconstrictive effect, blocking their action eases the condition of patients and makes them breathe easier. Some patients develop Churg-Strauss syndrome, consisting of eosinophilia, eosinophilic pneumonia, and vasculitis, after using montelukast or zafirlukast, and must be treated with corticosteroids.

Attacks of bronchial asthma and exacerbations of chronic obstructive disease are treated with parenteral or oral administration of corticosteroids, which powerfully reduce inflammation and stop the attack or exacerbation. In an attack, short-acting beta 2 agonists can be administered in the form of inhalation (salbutamol), as well as aminophylline injections (theophylline in ethylene-di-amide), which, due to the blockade of phosphodiesterase and the activation of adenosine receptors, leads to bronchodilation; in the most severe cases, a subcutaneous injection of adrenaline can also be used, which also widens the airways by acting on beta 2 receptors, but also reduces swelling of the mucous membrane due to vasoconstriction, after acting on alpha 1 receptors.

EXPECTORANTS

Expectorants are drugs used to facilitate the expectoration of thick secretions. We can use natural medicines such as primrose tea or ivy tea, Hedera helix (both plants contain saponins, which have an irritating effect on the mucous membrane of the stomach and reflexively cause coughing), and synthetic bromhexine or its derivative ambroxol, in the form of tablets. Instead of expectorants, we can also use mucolytics for easier expectoration, which dilute secretions with their sulfhydryl groups. The most important preparation we use is acetylcysteine. However, mucolytics should not be used by people with gastric or duodenal ulcers, because they also break down the protective layer of mucus in these organs, and can lead to bleeding.

ANTITUSSIVES

Antitussives are medicines that suppress a persistent, dry cough. In small children, a significant antitussive effect is also achieved by ordinary syrup, i.e., concentrated solution of sugar in water. Antitussives with a central effect, such as butamirate or codeine, are mostly used in the elderly. The problem with antitussives with a central effect is the possibility of respiratory depression, so they should be avoided in people whose breathing is otherwise compromised (e.g., in severe forms of chronic obstructive pulmonary disease). A milder form of dry cough can be treated with harmless marshmallow tea, which contains mucous substances that coat the mucous membrane and prevent irritation of nerve endings.

OXYGEN

Oxygen is most often administered in a concentration of 28% through a mask or nasal catheters, at a rate of 4-6 l/min. The use of 100% oxygen should be avoided and limited in time, because prolonged use leads to damage to the mucous membrane of the respiratory tract and the formation of tracheobronchitis with pronounced secretion, and even to damage to the lungs themselves. We administer oxygen whenever there is hypoxia, but we should be careful in patients with chronic obstructive pulmonary disease who have been cyanotic for a long time. These patients breathe only based on the registration of oxygen levels in the blood, because their respiratory center has become insensitive to carbon dioxide. When we give them oxygen, they can stop breathing, so they need special care when applying oxygen.

PHARMACOLOGY OF THE GASTROINTESTINAL TRACT

EMETICS AND ANTIEMETICS

The most effective remedy for inducing vomiting is syrup of ipecac. One large spoonful of syrup is enough to induce vomiting after 10 minutes. If we do not have ipecac, we can induce vomiting with a subcutaneous injection of apomorphine. Unfortunately, these

preparations are not regularly available on the market in our country. Vomiting must not be induced when the patient is unconscious (the vomited contents could be aspirated and suffocate the patient), when he is poisoned by acids or bases (the esophagus could rupture), when he is poisoned by oil and its derivatives (if vomited content is inhaled, it results in aspiration pneumonia with high mortality) or when poisoned with substances that cause an epileptic attack (e.g., cocaine, because vomiting can provoke an epileptic attack).

Vomiting caused by driving any form of transport can be prevented by taking an H1 antihistamine such as diphenhydramine one hour before travel by oral route. Such vomiting can also be prevented by the use of transdermal patches containing scopolamine.

Vomiting after surgery or in mild diseases of the gastrointestinal tract can be stopped by the administration of metoclopramide, orally or parenterally, which blocks dopamine receptors in the vomiting center. Compared to metoclopramide, the corticosteroid dexamethasone is significantly more effective in preventing postoperative vomiting.

Vomiting due to the use of cytostatics is prevented by the administration, one hour before cytostatics, of drugs that block serotonin 5-HT3 receptors. Examples of drugs from this group are ondansterone and granisetrone. Combinations of 5-HT3 receptor blockers and dexamethasone are currently used in the treatment of vomiting that occurred after the use of cytostatics.

TREATMENT OF PEPTIC ULCER

To cure a peptic ulcer we need to do two things: to reduce acid secretion and to destroy Helicobacter pylori. Acid secretion is reduced by six-week administration of proton pump blockers (pantoprazole, lansoprazole, etc.), which almost completely stop acid secretion from the parietal cells. We destroy Helicobacter by simultaneously applying two antibiotics; most often we use amoxicillin, clarithromycin or metronidazole. Sometimes a preparation of bismuth is added to antibiotics. Antimicrobial therapy of peptic ulcer lasts 7-14 days. The doctor is obliged to test the presence of Helicobacter pylori before starting the treatment, and to confirm that Helicobacter is no longer present with the same test after the treatment is completed. Today, the test for Helicobacter pylori in stool is used as the most reliable. Previously, instead of proton pump blockers, histamine H2 blockers (ranitidine, famotidine) were used to reduce acid secretion, but they can reduce acid secretion by 70% at most. Today, proton pump blockers have an advantage because they are more effective in reducing acid secretion than H2-blockers. It is important to prevent the prolonged use of proton pump blockers (over 6 weeks), because then serious side effects are manifested: a higher frequency of pneumonia and the occurrence of interstitial nephritis.

TREATMENT OF SPASMS IN THE BILIARY, URINARY AND GASTROINTESTINAL TRACT

Spasms always occur when there is some obstruction in the biliary, urinary or gastrointestinal tract. They cannot be eliminated until the obstruction is removed, but they can be alleviated by the use of antispasmodics. Spasms are treated using muscarinic receptor blockers, scopolamine butyl bromide or propantheline, which relax smooth muscles. Spasms can also be treated using calcium channel blockers, e.g., nifedipine, but we have to be careful not to decrease too much blood pressure. Also recently, alpha 1 blockers have been used to treat spasms in the ureter, in order to relax the lower part of the ureter and facilitate the elimination of the stuck stone.

TREATMENT OF CONSTIPATION

A person is considered to be constipated if they have less than 3 bowel movements per week. Constipation is best treated with the use of plant fibers (e.g., wheat bran) and increased fluid intake, as these measures increase the volume of bowel contents and thus cause emptying. When a quick emptying of the bowels is needed (that is, we cannot wait a day or two for the plant fibers to start working), we can use osmotic laxatives, which attract water and therefore expand the bowel lumen, causing emptying. The best-known osmotic laxatives are magnesium sulfate (bitter salt) and lactulose. There is also a group of laxatives that irritate the intestinal wall, such as bisacodyl or anthraquinone preparations from plants. These drugs work after a latent period of 6-8 hours, by stimulating neurons in the wall of the large intestine. Irritant laxatives should not be used by patients for a long period of time, because there is a suspicion that they damage the neurons in the intestinal wall, so over time first dependence develops, and then tolerance, and the mucous membrane of the colon becomes darkly pigmented (melanosis of the colon).

ANTI-DIARRHOICS

Diarrhea of infectious origin is not treated with antidiarrheal drugs, but only by replenishment of the patient's fluid and electrolytes, and in case of invasive infections, we also apply antibiotics (invasive infection: the patient has a fever, blood and mucus in the

stool). We use antidiarrheals only for diarrhea that does not have an infectious cause. We use loperamide, a drug that stimulates opioid receptors, causing a slowdown in bowel motility. Another option is to use diphenoxylate, a drug that blocks muscarinic receptors and thus slows down intestinal motility.

ANTIMICROBIAL THERAPY

PRINCIPLES OF APPLICATION OF ANTIBIOTICS

Antibiotics are drugs that destroy microorganisms (bactericides) or stop their reproduction (bacteriostatics), by interfering with the metabolic and growth processes of microorganisms.

The principles of antibiotic use are as follows:

1. We apply them only if we are sure that they are bacterial infections or infections caused by mycoplasmas, chlamydia or rickettsiae.

2. We administer antibiotics immediately after the diagnosis of a bacterial infection, because delaying would lead to a worsening of the patient's condition (such an approach is called "empirical administration"), but before the first dose, we must take a sample of fluid or tissue and send it to a microbiological laboratory for isolation of the causative agent and examination of sensitivity ("antibiogram").

3. The antibiotic must show its effect no later than the third day after the start of administration. If the patient's condition is better on the third day, we continue with the same antibiotic. If the patient's condition is worse or the same, we have to change the antibiotic. That's why the golden rule for the general practitioner applies: "If one has prescribed an antibiotic to a patient, he/she must schedule a follow-up in three days."

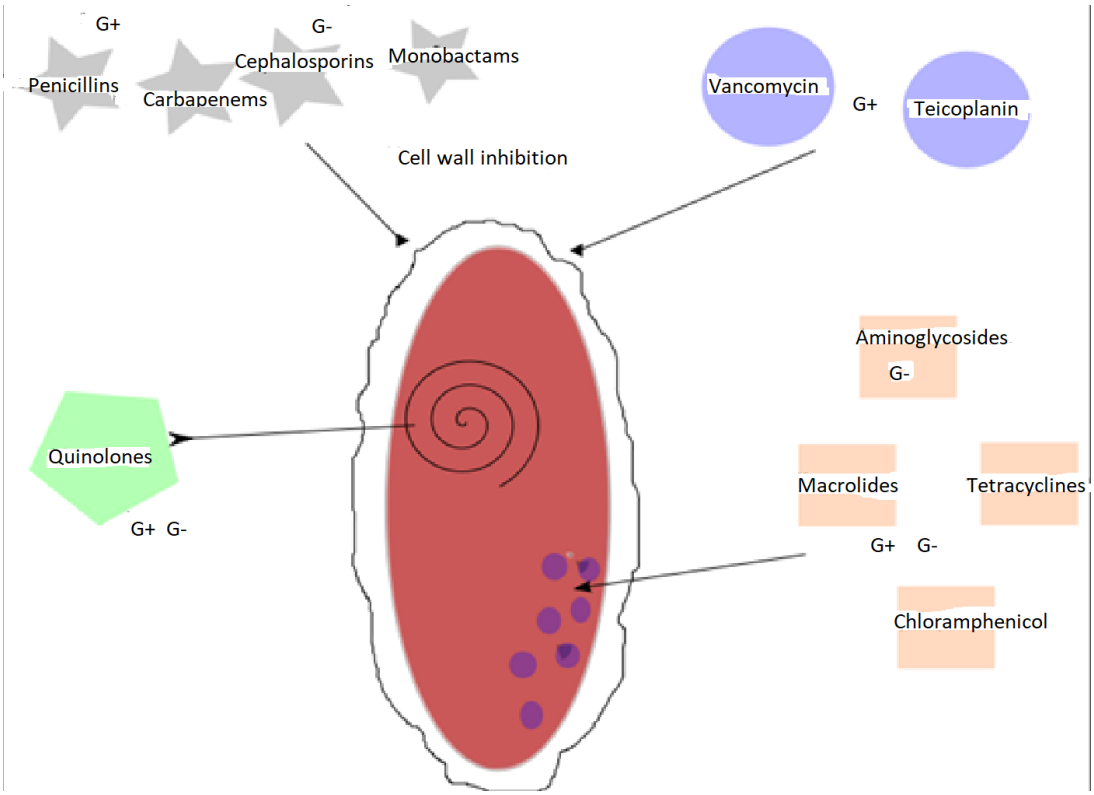
4. Antibiotics alone cannot bring about a cure if the patient has an abscess or a foreign body. It is necessary to drain the abscess and remove the foreign body.

Prophylactic use of antibiotics

Prophylactic use of antibiotics means use before an infection has occurred. It is justified in the following cases:

1) Before surgical intervention in which a foreign body is implanted in the patient or one of the larger organs is removed (for example, the large intestine); only one dose is applied about an hour before the first cut on the skin.
2) During dental interventions, in patients who have suffered from rheumatic fever or have a disease of the heart valves.
3) Application in patients whose spleen was removed due to injury, at least one year after the operation.
4) In persons living in the same family with a tuberculosis patient.

Figure 7. Mechanism of action of antibiotics. Beta lactams (marked by stars) and glycopeptides (marked by circles) interfere with cell wall synthesis, quinolones (marked with a pentagon - ciprofloxacin, levofloxacin and moxifloxacin) interfere with DNA transcription, while aminoglycosides, macrolides, tetracyclines and chloramphenicol (marked with squares) interfere with protein synthesis in the bacterial cell. .



BETA-LACTAM ANTIBIOTICS

There are four groups of beta-lactam antibiotics: **penicillins, cephalosporins, carbapenems and monobactams**.

All of these antibiotics have a beta-lactam ring in their molecule, and they all work by preventing the synthesis of the bacterial cell wall. Due to the similar chemical structure, there is a problem of **cross-allergic** reactions when using these drugs. This means, if someone becomes allergic to one of the drugs from these groups, there is a significant probability that he/she is also allergic to the others (from 1 to 8%). That's why we have to administer antibiotics from other groups to such patients, which are not beta-lactams.

Penicillins

We divide them into natural and semi-synthetic. Of the natural penicillins, the most important are penicillin G (benzylpenicillin), which is given intravenously or intramuscularly as a depot preparation (a mixture of benzyl penicillin and procaine-benzylpenicillin), and penicillin V (phenoxymethylpenicillin), which is given orally. Today, natural penicillins are mostly used to treat streptococcal infections (tonsillitis, cellulitis) and infections caused by clostridia (the cause of gas gangrene).

Of the semi-synthetic penicillins, two groups are important:

A) semi-synthetic penicillins resistant to penicillinase, an example is cloxacillin, which is used to treat staphylococcal infections, because staphylococci produce beta-lactamase; unfortunately, penicillins from this group are not available for use in Serbia.

B) semi-synthetic penicillins with a wide spectrum of action. The most important drug from this group is amoxicillin. Amoxicillin acts, in addition to streptococci, on gram-negative bacteria such as Proteus and Escherichia coli, and Haemophilus influenzae. That's why amoxicillin is used to treat infections of the oral cavity, middle ear, sinuses, respiratory tract, and urinary tract. Amoxicillin is often supplemented with a preparation of clavulanic acid that inhibits beta-lactamase, so the combination of amoxicillin and clavulanic acid is used to treat more severe infections than amoxicillin alone, and it is especially good for preventing infections after bites by dogs, other animals or humans. If amoxicillin is administered to a person who has a viral infection (especially infectious mononucleosis), the appearance of skin rash can be expected. Also, higher doses of clavulanic acid are associated with hepatotoxicity. A special subgroup consists of semi-synthetic penicillins

with an extended spectrum of action, such as piperacillin, which also act on bacteria prone to resistance (e.g., Klebsiella or Pseudomonas); their effectiveness is further increased by combining it with the beta-lactamase inhibitor tazobactam.

Cephalosporins

Cephalosporins are divided into five generations based on the time of their synthesis and spectrum of action.

We use the **first generation** (**cephalexin** - oral administration, **cefazolin** - parenteral) for infections caused mainly by gram-positive bacteria (e.g., skin and subcutaneous tissue infections, respiratory infections, prophylaxis of infections in surgery with cefazolin).

Second-generation cephalosporins (**cefachlor** - oral, **cefuroxime** - parenteral) are used for mild infections caused by gram-positive and gram-negative bacteria (e.g., sinusitis with cefachlor, prophylaxis of infections in surgery with cefazolin).

We use **third-generation cephalosporins** (**ceftriaxone** and **ceftazidime**) only for serious infections caused by gram-negative bacteria. They are administered parenterally, and are used in hospitals to treat urinary, intra-abdominal, respiratory and central nervous system infections. Ceftazidime works particularly well against Pseudomonas aeruginosa. In order to extend their effect on bacteria that produce beta-lactamases, they are combined with beta-lactamase inhibitors: ceftazidime with avibactam, and ceftolozane with tazobactam.

We use **fourth-generation cephalosporins** (cefepime) only for the most severe infections with both gram-positive and gram-negative bacteria. Cefepime penetrates the bones, lungs and central nervous system very well, so it has proven to be successful in the treatment of infections in those regions.

The **fifth generation** consists of the cephalosporin **ceftaroline**, which, in addition to its effect on a large number of gram-positive and gram-negative bacteria, has a strong effect on methicillin-resistant staphylococcus, so today it is mainly used for infections with that pathogen, especially on the skin, subcutaneous tissue and lungs.

Carbapenems

Carbapenems are beta-lactams with a very broad spectrum of action. They act on a large number of gram-positive and gram-negative bacteria, but also on anaerobic bacteria, which is not the case with cephalosporins. Ertapenem, meropenem and imipenem with cilastatin (cilastatin prevents the breakdown of imipenem in the kidneys) are antibiotics from this group that are given parenterally for the most severe infections of the abdomen, pelvis, skin and subcutaneous tissue of pneumonia, as well as for sepsis. Unlike meropenem and imipenem, ertapenem does not work against Pseudomonas aeruginosa, so it is only used for infections that start outside the hospital, where the frequency of that bacterium is much lower. Carbapenems are well tolerated, only in rare patients they can provoke an epileptic attack (ertapenem and imipenem) or cause liver cell damage (meropenem). They are administered exclusively intravenously.

Monobactams act only on gram-negative bacteria; their main representative, aztreonam, is not approved for use in our country.

TETRACYCLINES

Tetracyclines prevent protein synthesis in bacteria. They have a very wide spectrum of action because they act on gram-positive, gram-negative bacteria, mycoplasma, chlamydia and rickettsia. We use doxycycline, which is given orally once a day and is excreted through the bile, and tetracycline (and similar antibiotics) which is excreted through the kidneys, and is given orally for 6 hours. Tetracyclines are known to cause nausea and vomiting, and we must not give them to children under 12 years old, so that they do not settle in tooth enamel and bones. A good feature of tetracyclines is that they rarely interact with other drugs, and that they do not have a proarrhythmogenic effect, so they can be given to elderly people with heart disease.

Tetracyclines should not be taken together with milk and milk products, because calcium from these foods forms insoluble complexes with tetracyclines that cannot be absorbed.

MACROLIDE ANTIBIOTICS

This group includes **erythromycin, azithromycin, clarithromycin and roxithromycin**. Macrolides prevent protein synthesis in bacterial cells and thus stop their growth. They work well on gram-positive bacteria, mycoplasma, chlamydia, rickettsia and legionella (the bacterium that causes Legionnaires' disease). In practice, we mostly use these drugs for the treatment of respiratory infections, especially pneumonia that the patient gets outside the hospital, and for the eradication of Helicobacter pylori (the cause of ulcers). Of these, erythromycin has the most side effects, which can cause vomiting in children and sometimes liver damage (this happened especially with erythromycin-estolate salt, while it is very rare with erythromycin-ethylsuccinate, which is used far more today).

Clindamycin is similar to macrolides and works well on infections caused by staphylococcus and anaerobic bacteria. It is especially good for the treatment of staphylococcal bone infections (because it penetrates the bone well) and for the treatment of head infections, especially those originating from the oral cavity. Clindamycin somewhat more often than other antibiotics causes an overgrowth of the anaerobic bacterium Clostridium difficile, which results in colitis and diarrhea. It can also lead to liver cell damage in a number of people.

CHLORAMPHENICOL

Chloramphenicol is an old antibiotic with an extremely broad spectrum of action, which was once thought to be able to cure almost all infections (it was called the "magic bullet"). Chloramphenicol inhibits protein synthesis in bacteria and acts on gram-positive, gram-negative bacteria, rickettsia and mycoplasma, but does not act on chlamydia and even worsens infections caused by these pathogens. Although it is very effective and penetrates well into all parts of the body, we rarely use chloramphenicol, only when there is no possibility of using another antibiotic. The reason for this is its myelotoxicity: in a significant percentage of patients, chloramphenicol causes leukopenia, thrombocytopenia, and very rarely it can cause aplastic anemia. Also, in premature children and newborns in general, the use of chloramphenicol in larger doses due to immature metabolic pathways in the liver and slow elimination leads to the accumulation of the drug and the appearance of "gray baby syndrome" (hypotension, pale-cyanotic skin, abdominal distension and death in a few hours). Today, we most commonly use chloramphenicol to treat central nervous system infections that have not responded to other antibiotics.

AMINOGLYCOSIDES

Aminoglycosides are antibiotics with large, polar molecules that inhibit protein synthesis in bacterial cells. They have a relatively narrow spectrum of action, because they act only on gram-negative bacteria (E. Coli, Proteus, Klebsiella, Pseudomonas), and to a lesser extent on the streptococcus and staphylococcus. That's why we use them only for the treatment of urinary tract infections or for more severe infections of internal organs in combination with beta-lactam antibiotics (with which they act synergistically). They are administered only parenterally, because due to the polarity of their molecules, they cannot be absorbed from the intestine. The main representatives are **amikacin, gentamicin and tobramycin**. The most important side effects of aminoglycosides are kidney damage (nephrotoxicity) and inner ear damage (ototoxicity).

Aminoglycosides act on bacteria more effectively if their concentration in the blood is higher; therefore, they are administered in one daily dose, which represents the sum of the doses that would normally be given every 8 hours.

SULFONAMIDES

Sulfonamides are compounds in which a sulfate group is attached to an amino group in the molecule. They interfere with folic acid synthesis in bacteria by interfering with the reduction of para-aminobenzoic acid to dihydro-pteroate. Sulfonamides were once much more widely used for the treatment of bacterial infections, and today we mostly use the combination of sulfamethoxazole with trimetaprim (these two drugs lead to the so-called sequential block of the synthesis of tetrahydro-folic acid, because sulfamethoxazole blocks the synthesis of folic acid, and trimethoprim the reduction of dihydro-folic acid to tetrahydrofolic acid), which is called „Bactrim“ or co-trimoxazole. Bactrim is mostly used to treat respiratory and urinary tract infections. The dosage is always 2 tablets per day (each tablet contains 400 milligrams of sulfamethoxazole and 80 milligrams of trimethoprim). In addition to co-trimoxazole, sulfacetamide in the form of eye drops, silver-sulfadiazine to prevent secondary infection of burns, sulfasalazine to treat inflammatory bowel diseases and sulfisoxazole to treat urinary tract infections are used today.

Sulfonamides have a wide range of effects, but resistance to them develops relatively quickly. In addition to bacteria, they act on the causative agents of malaria and toxoplasmosis. They are partly metabolized in the liver, and the metabolites are excreted in the urine.

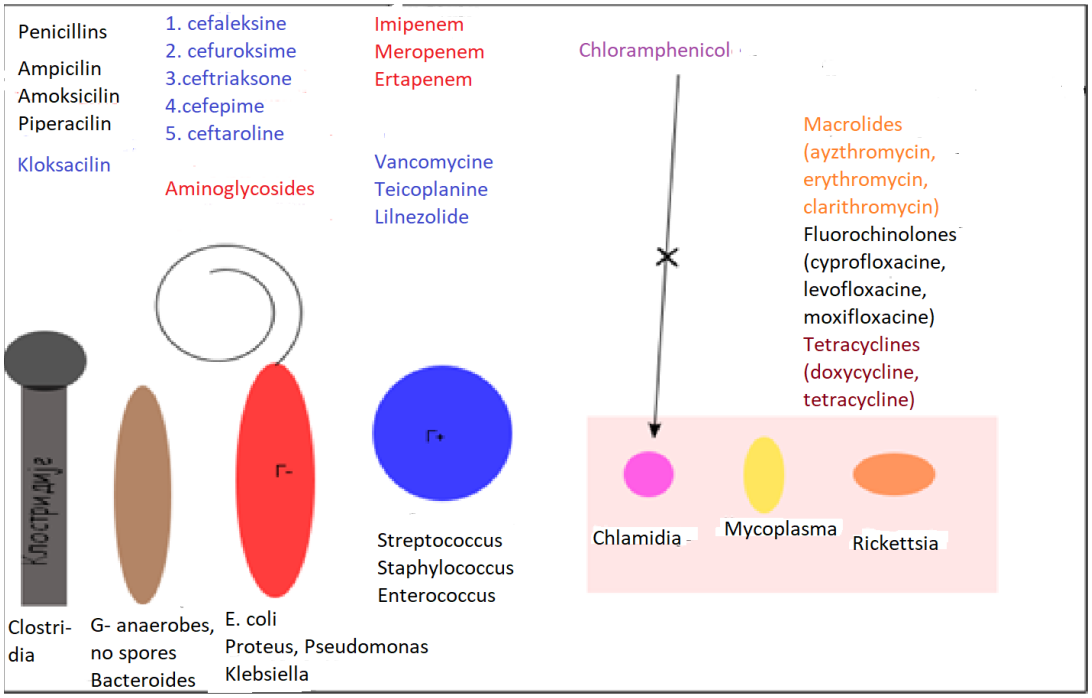
We avoid sulfonamides in pregnant women, nursing mothers and children younger than 2 months, because they displace bilirubin from albumin, leading to hyperbilirubinemia and kernicterus, i.e., damage to the basal ganglia in the brain. Also, sulfonamides can cause damage to the bone marrow, kidneys and severe bullous skin rash in other patients. To prevent kidney damage, patients taking sulfonamides should drink plenty of fluids and ensure a diuresis of at least 1.5 liters of urine per day.

QUINOLONES

Quinolones are antibiotics that interfere with the functioning of bacterial DNA by blocking the enzyme DNA gyrase. They used to be classified to **non-fluorinated ones,** such as pipemidic acid**,** which achieved effective concentrations only in urine (they were called uroantiseptics)**,** and **fluorinated** quinolones, which achieve good concentrations in all tissues, so they are used to treat systemic infections. However, pipemidic acid has recently been withdrawn from use, while fluorinated quinolones are still used, but with restrictions. Fluoroquinolones have a wide range of effects, they act on gram-positive, gram-negative bacteria, mycoplasma, rickettsia and chlamydia; only they do not work on anaerobic bacteria. The most important fluorinated quinolones are: **ciprofloxacin** (used to treat urogenital tract infections and traveler's diarrhea), **levofloxacin** (used to treat community-acquired pneumonia) and **moxifloxacin** (used for community-acquired pneumonia, but also for complicated skin and soft tissue infections). These drugs are administered both orally and intravenously; ciprofloxacin is eliminated the fastest, so it is administered in several daily doses, while levofloxacin and moxifloxacin are usually administered once a day.

The use of fluorinated quinolones is currently limited only to the treatment of infections for which there is no suitable alternative antibiotic therapy, because their side effects can have permanent consequences. First of all, fluoroquinolones lead to disorders of the functioning of the connective tissue, so tendon ruptures occur in some patients, even months after the cessation of their use. They damage the nervous system, leading to peripheral neuropathy, depression, impaired hearing, vision and sense of smell. They are not used in pregnancy because they are teratogenic, nor in children because they interfere with the growth of joint cartilages. In addition to all that, they tend to cause a disturbance of the intestinal flora and diarrhea, and even colitis due to the overgrowth of Clostridium difficile which secrete toxins.

Figure 8. Spectrum of antibiotic action.



GLYCOPEPTIDES

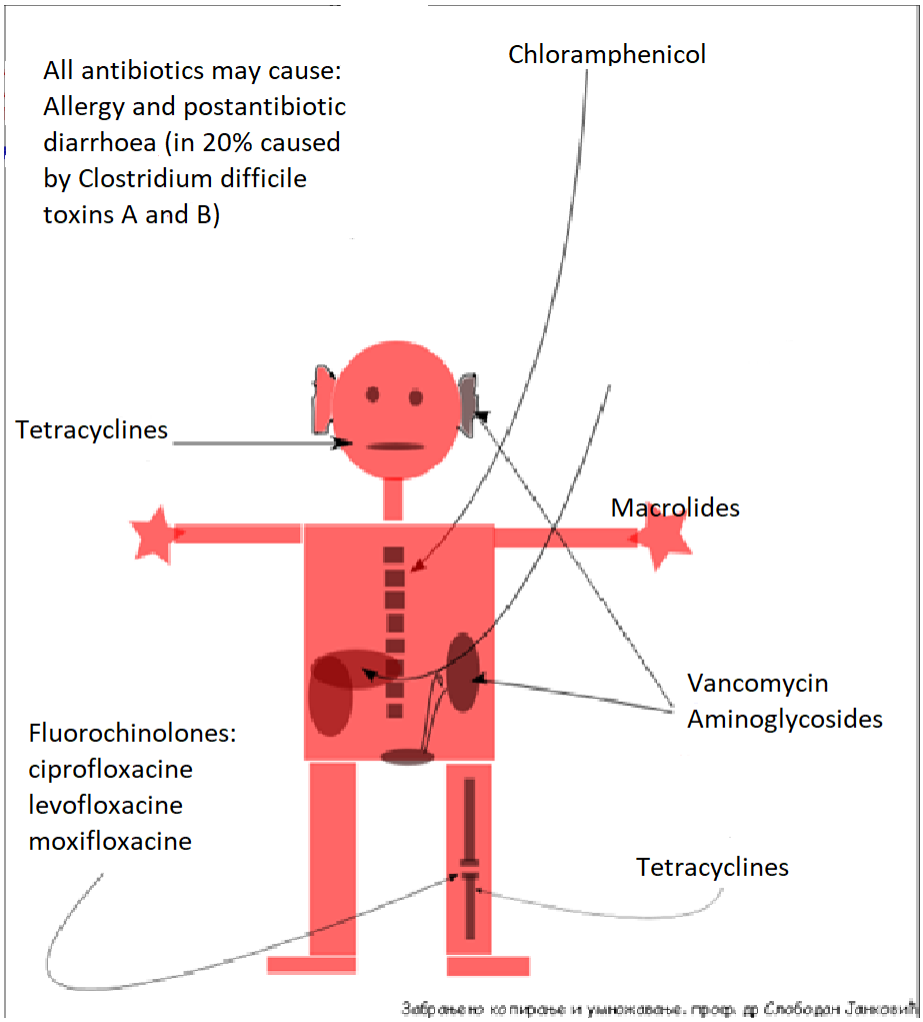
The glycopeptide antibiotics vancomycin and teicoplanin have large polar molecules and are administered only intravenously in hospital settings, primarily for the treatment of infections caused by methicillin-resistant staphylococcus and enterococci. The mechanism of action of these antibiotics is to interfere with the synthesis of the bacterial cell wall. Both antibiotics are nephrotoxic and ototoxic. Glycopeptides are not metabolized in the liver, but excreted unchanged in the urine. When vancomycin is given by infusion, the infusion must last at least 2 hours, in order to avoid the " **red man syndrome** " - redness of the face, neck and chest. Vancomycin can also be used orally, but only for the treatment of pseudomembranous colitis caused by Clostridium difficile .

METRONIDAZOLE

Metronidazole is a drug that acts only on anaerobic bacteria (Bacteroides, Clostridium, Fusobacterium), facultatively anaerobic infections (Gardnerella vaginalis, Helicobacter pylori), amoeba and trichomonas. Metronidazole is reduced in the cells of the causative agent of the infection, which further increases the entry of metronidazole and the formation of free radicals; free radicals damage DNA and lead to the death of bacteria or protozoa. Metronidazole is used for the treatment of infections in the oral cavity, for the elimination of Helicobacter pylori, for the treatment of complicated intra-abdominal infections, bacterial vaginosis, colitis caused by Clostridium difficile, amoebic dysentery, trichomonas infection of the genital organs and other protozoal infections of the small and large intestines (giardiasis and balantidiasis). In the treatment of these infections metronidazole can be administered orally or intravenously.

When the patient is taking metronidazole, he must not consume alcohol, because the drug inhibits aldehyde dehydrogenase and leads to the accumulation of acetaldehyde and the so-called "disulfiram reaction", i.e. nausea, facial redness, feeling hot, sometimes vomiting. Prolonged use of metronidazole leads to neuropathy.

Figure 9. Side effects of antibiotics.



TREATMENT OF TUBERCULOSIS

Tuberculosis is not easy to cure: it is hard for a drug to reach the Mycobacterium tuberculosis because it is inside the human cells. Therefore, it is necessary that the therapy lasts at least 6 months. Also, due to the high propensity of tuberculosis bacilli to become resistant to the drug used as monotherapy, patients with this disease are always treated with a combination of four drugs for the first two months, and then patients take two drugs for the remaining 4 months. First-line antituberculosis drugs are isoniazid (prevents the synthesis of the cell wall of mycobacteria; vitamin B6 must be taken with isoniazid to

prevent neurotoxic effects; isoniazid is also hepatotoxic), rifampicin (blocks RNA synthesis in mycobacteria; it is hepatotoxic and turns urine orange; induces the metabolism of drugs in the liver, which weakens their effect), ethambutol (also inhibits the synthesis of the cell wall; can cause inflammation of the optic nerve) and pyrazinamide (the mechanism of action is not clear, but it works especially well on intracellular bacilli; it is very hepatotoxic). Ethambutol and pyrazinamide are given only for the first two months of therapy, while isoniazid and rifampicin are given for all 6 months.

ANTIBIOTICS EFFECTIVE AGAINST TEETH AND ORAL CAVITY INFECTIONS

Certain dental interventions have an invasive character, leading to the entry of bacteria from the oral cavity into the bloodstream, i.e., to bacteremia. Such interventions include tooth extraction, operations in the oral cavity, removal of subgingival calculus, restorative interventions, placement of orthodontic appliances and other interventions where bleeding occurs or where work is done on infected tissue. If the person undergoing dental intervention is immunocompromised or has some tissue damage, bacteria from the blood can settle on distant organs and cause a systemic infection with serious consequences. In order to prevent this, such patients are given antibiotic prophylaxis before the aforementioned interventions.

Categories of patients who should be given antibiotic prophylaxis before invasive interventions in dentistry are: patients with previous bacterial endocarditis, patients with artificial heart valves, rheumatic heart disease in the past, patients with congenital anomalies of the heart, mitral valve prolapse with mitral insufficiency, presence of intravenous or intra-arterial catheters, patients in immunosuppression, patients with ventriculo-peritoneal or ventriculo-atrial shunt due to hydrocephalus, and some other categories.

As a standard prophylaxis, an adult patient should be given 2 grams of amoxicillin orally (children 50 mg/kg) one hour before surgery. If the patient is allergic to penicillin, clindamycin 600 mg orally (children 20 mg/kg) should be given one hour before surgery, or azithromycin 500 mg (children about 15 mg/kg).

Some dental infections (pulpitis, periapical periodontitis, localized dentoalveolar abscess, plaque-induced gingivitis) should not be treated with antibiotics, but with interventions such as incision, root canal treatment or local irrigation. On the other hand, more severe infections such as pericoronitis, lateral periodontal abscess and facial cellulitis should be treated with both antibiotics and surgery. The antibiotic of choice for dental and oral cavity infections is amoxicillin 500 mg every 8 hours, orally. In patients who have recently received antibiotics, it is better to give amoxicillin with clavulanic acid. If the

patient is allergic to penicillin, the drug of choice is clindamycin (150 to 450 mg every 6 hours orally) or metronidazole 200 mg every 8 hours. If the patient has ulcerative gingivitis, pericoronitis or periodontal abscess, it is better to use metronidazole 250 mg every 8 hours.

A combination of amoxicillin and metronidazole is used in the treatment of apical abscess and pericoronitis. Actinomycosis of the oral cavity is treated with amoxicillin or doxycycline for an extremely long time, about 6 weeks, because the antibiotics slowly penetrate the actinomycosis foci that have changed into scars. For staphylococcal lymphadenitis in the submandibular region, the best choice is the use of clindamycin.

A special problem with infections of the oral cavity (especially molar root infection) is the possibility of their spreading through the floor of the oral cavity to the neck, and further to the mediastinum (middle chest). Bacterial infections spread rapidly in these areas; an infection accompanied by a large swelling that affects the oral cavity and spreads to the neck is called Ludwig's angina. The most common causes of Ludwig's angina are streptococci, staphylococci and anaerobic bacteria of the Bacteroides type, so the treatment uses a combination of large doses of crystalline penicillin G in the form of intravenous infusion, and clindamycin or metronidazole.

In chronic periodontitis, an antibiotic can be applied locally (in the gingival "pockets") if good plaque control has been achieved and the periodontium is still inflamed. First, debridement of the tooth root (removal of biofilm) is performed, and then an antibiotic is applied locally in the form of paste, gel or impregnated fibers. Locally applied are minocycline, tetracycline, metronidazole and antiseptic chlorhexidine. Minocycline and tetracycline are thought to act not only antibacterially, but also to prevent the breakdown of alveolar bone due to the inhibition of matrix-metalloproteinases secreted by bacteria. In clinical studies, the local application of antibiotics did not show significant effectiveness, so in more severe conditions, systemic administration of antibiotics is advised: tetracycline or amoxicillin in combination with metronidazole.

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 to 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 the common 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", $KMnO_4$) in a dilution of 1:5000 is used 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 a tenfold greater dilution (0.3%), hydrogen peroxide can be used to rinse the oral cavity and oropharynx.

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: 6.5g of iodine + 2.5g of potassium iodide + 91g 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 povidone-iodine, solution and foam, are used to clean the skin. 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 sodium chloramide, 0.25-0.5%) has a similar function, which can also be used to disinfect objects and floors (1-5%).

VI) **Detergents**. Detergents are surface-active substances whose cationic part penetrates the membrane of microorganisms and destroys it. The cationic part almost always contains quaternary nitrogen. Benzalkonium chloride and other detergents are primarily 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) has been 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 to disinfect objects and, in the absence of better means, to quickly disinfect the 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 as a solution (2%) which must be alkalinized (pH around 8) to be activated.

ADVERSE EFFECTS OF ANTISEPTICS AND DISINFECTANTS

An antiseptic is a substance that reduces the number of microorganisms on the skin or mucous membranes of a person. A disinfectant is a substance that reduces the number of microorganisms on objects, and a sterilant is a substance that destroys all microorganisms and their spores on objects.

Chlorhexidine causes gastrointestinal irritation. In larger doses, it causes damage to the liver and lungs. Intravenous administration and inhalation cause methemoglobinemia and hemolysis.

Hydrogen peroxide (H_2O_2) acts as a local irritant. If inserted into a deep wound, it can release oxygen and create a gas embolism. If drunk, it only causes nausea and vomiting. When hydrogen peroxide is drunk, gas should be removed from the stomach by nasogastric suction. A patient with a pulmonary artery gas embolism should be immediately placed in the Trendelenburg position and immediately sent to a hyperbaric chamber.

Iodophors are substances in which iodine is bound to a high-molecular carrier, which enables greater solubility (e.g., povidone). After ingestion, iodine and iodophors have a caustic effect: they cause pain, vomiting, diarrhea, hypovolemia and shock. The patient should immediately be given starch solution or milk, because in contact with them, iodine turns into less toxic iodides; the contents of the stomach become dark purple. Activated charcoal should also be used.

Potassium permanganate ($KMnO_4$) is a strong oxidizing agent. If drunk, it acts caustic; in contact with water it decomposes into MnO_2, KOH and O_2. Manganese dioxide stains tissues black-brown. Due to its oxidative effect, it causes methemoglobinemia, hemolysis, liver and lung damage. Potassium permanganate poisoning is treated like base poisoning.

Chlorine gas causes lung damage. Taking chlorine preparations orally has a caustic effect on the stomach and esophagus.

Formaldehyde is usually found in a water-alcohol solution (37% formaldehyde, 12-15% methanol). If taken orally, it is caustic. As it is absorbed, formaldehyde turns into formic acid and causes severe acidosis. Sodium bicarbonate should be administered to control acidosis. Treat local changes as in the case of ingestion of acids or bases.

Phenol has a caustic effect in the gastrointestinal tract. It acts as a stimulant in the CNS. Symptoms and signs of poisoning are: convulsions, lethargy, coma, acidosis, methemoglobinemia, abdominal pain, vomiting and perforation. If spilled on the skin, it turns pale brown. Decontamination of the skin should be done with low-molecular polyethylene glycol (PET 300 or 400).

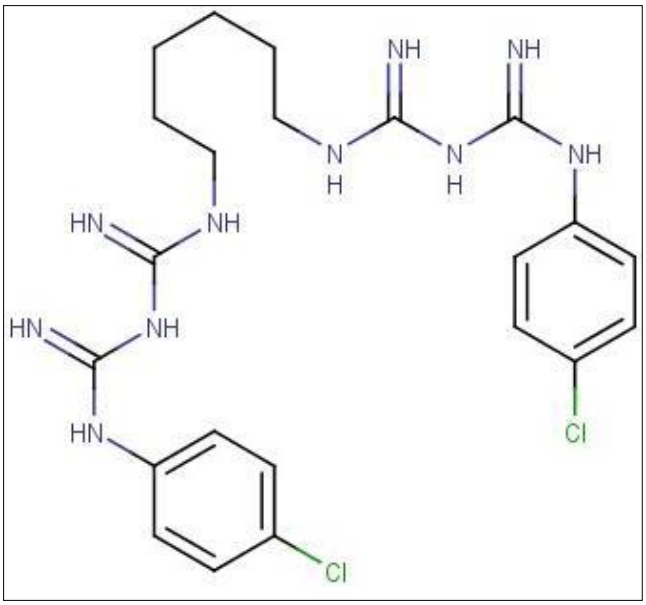
Hexachlorophene (chloro-phenol) and cresols (methyl-phenols) are caustic, causing hemolysis, kidney and liver damage, and CNS depression. Chronic use of hexachlorophene in infants results in vacuolar encephalopathy.

Glutaraldehyde is a liquid used to sterilize optical instruments and dental equipment. The poisoning is very similar to formaldehyde poisoning, so it is treated in the same way.

Boric acid (H_3BO_3) is obtained from borax ($Na_2B_4O_7*10H_2O$) and is used as a poison for cockroaches. If drunk, it acts as a local irritant (abdominal pain, vomiting, diarrhea - green-blue content). The patient is all red, it looks like "cooked lobster". Rash is especially present on the soles, palms and buttocks; desquamation occurs after 1-2 days. Kidney damage can also occur. Alopecia occurs with chronic exposure. In case of boric acid poisoning, activated carbon is not worth using, because it does not bind to this acid. Hemodialysis may be beneficial.

ANTISEPTICS USED IN THE ORAL CAVITY

Antiseptics are used in toothpastes and other preparations to prevent the formation of bacterial plaque. Bis-biguanide antiseptics (chlorhexidine), quaternary ammonium compounds (cetylpyridinium and benzalkonium chloride), phenols, oxidizing agents, detergents and amino alcohols are used for this purpose. So far, chlorhexidine has shown the greatest effectiveness. To prevent plaque, antiseptics are used in the form of mouthwash, chewing gum and toothpaste. The most common concentration in which chlorhexidine is used is 0.12%, while cetylpyridinium is used in a concentration of 0.1%.



Chlorhexidine

Chlorhexidine sometimes causes the tongue to become brown, especially if there are substances in the food that are anions and have the property of color. It has a bitter taste, and in some patients it can lead to taste disturbances. Ulcers of the gastric mucosa and swelling of the parotid gland occur very rarely.

The above-mentioned antiseptics can be used for rinsing the postoperative wound, for the treatment of recurrent oral ulcerations, for the treatment of stomatitis due to dentures and for the disinfection of installed orthodontic appliances.

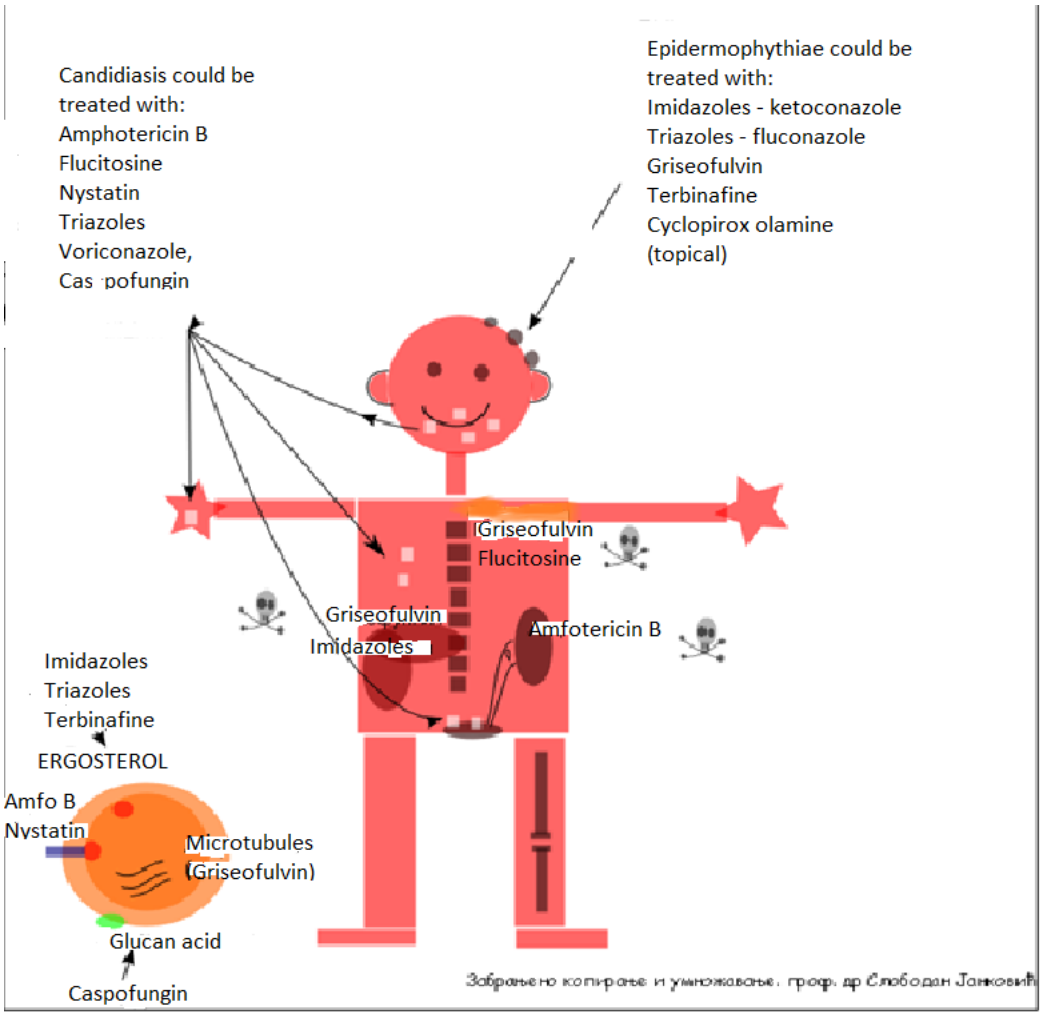
ANTIMYCOTICS

The fungi that most commonly infect humans are epidermophitia (which grow only on keratin and do not penetrate deeper through the skin), yeasts from the Candida and Pneumocystis jiroveci groups, Aspergillus mold and dimorphic fungi (they change from mold to yeast form and vice versa) Blastomyces and Histoplasma. In Serbia, infections with the species Blastomyces and Histoplasma are practically not encountered, while there are other fungal infections. Candida infections usually affect the mucous membranes, and in immunodeficient and decrepid patients, they penetrate the bloodstream and cause sepsis. Pneumocystis jiroveci causes pneumonia in patients with acquired immunodeficiency syndrome, and Aspergillus mold infects the lungs and other surrounding organs, not respecting the boundaries between tissue compartments.

Skin infections with epidermophytes can be treated with oral griseofulvin or terbinafine for several months. However, griseofluvin is hepatotoxic and damages the bone marrow, and terbinafine can damage the liver, and that is why for the treatment of epidermophytes, we more often use local therapy with imidazoles (clotrimazole, econazole, miconazole). Imidazoles work by interfering with the synthesis of ergosterol in the fungal cell membrane.

Candida infections are treated locally (in the vagina, intestines, between the fingers, in the oral cavity) using nystatin, which is completely harmless because it is not absorbed from the site of application. Nystatin binds to ergosterol in the membrane of the fungus and creates holes in the membrane through which water enters, causing the fungus to burst. More severe forms of candidiasis (esophagitis, urinary infection, pneumonia, sepsis) are treated with systemic administration of triazoles (imidazoles with three nitrogen atoms in the pentacycle) - usually fluconazole. Fluconazole and other triazoles are hepatotoxic and interfere with the metabolism of other drugs. If there is resistance to triazoles, we apply echinocandins (caspofungin, anidulafungin), which interfere with the synthesis of 1-beta-glucan in the fungal cell wall. Echinocandins are well tolerated; in a small number of patients, they can have a hepatotoxic effect. In case of candidiasis that is resistant to both imidazoles and echinocandins, we use amphotericin B, a drug with the same mechanism of action as nystatin, but less toxic than it (although amphotericin B is also nephrotoxic), which is given intravenously as a last-line therapy. An exception to the rest are respiratory tract infections caused by Pneumocystis jiroveci, which do not respond to the mentioned antifungal drugs, but to drugs that disrupt the synthesis of tetrahydrofolic acid in the causative agent, co-trimoxazole and pentamidine.

Figure 10. Antifungal drugs.



ANTIVIRAL DRUGS

Viral infections that most often require treatment are: labial herpes, genital herpes, herpes zoster, cytomegalovirus eye infection, influenza, hepatitis B, hepatitis C, and acquired immunodeficiency syndrome (AIDS).

Today, labial and genital herpes are primarily treated with **acyclovir**, a drug that after activation with thymidine kinase blocks the DNA polymerase of the virus. Acyclovir can be administered both orally and parenterally, and it is excreted relatively quickly from the body via the kidneys, so it must be administered every 4-5 hours. When a patient is on acyclovir therapy, he needs to drink a lot of fluids, to avoid damage of the kidneys due to crystallization in the tubules. Acyclovir can be given both therapeutically and prophylactically in patients who have frequent relapses. We also treat herpes zoster with acyclovir, only in higher doses than herpes labialis or genital herpes.

Cytomegalovirus is present in many human beings, but it reactivates and causes retinitis only when the immune system is weakened, e.g., in the case of immunosuppression. It is treated with ganciclovir, a drug that after activation by phosphorylation inhibits the DNA polymerase of the virus. The treatment starts with intravenous administration of the drug, and then it continues orally. **Ganciclovir** has a deleterious effect on the bone marrow, leading to suppression of blood lines and consequent leukopenia or thrombocytopenia.

We treat influenza with antiviral drugs only in people in whom we expect a weak immune response and complications (elderly, immunocompromised, patients with comorbidities), in people who have been admitted for hospital treatment or in people with a very severe clinical picture. Influenza drugs include **oseltamivir,** which blocks viral neuraminidase and thereby virus entry into cells, and **baloxavir**, which inhibits endonuclease and RNA virus replication. Both drugs are administered orally. Oseltamivir in children can sometimes cause confusion and a tendency to self-harm, so this possibility should be taken into account.

For the treatment of hepatitis B, **interferon-alfa2a** is used, which is prepared as pegylated interferon-alfa, which means in the form of a depot preparation. The problem with the use of interferon-alpha is the fact that it sometimes causes depression, anemia and neutropenia. Immediately after the injection, the patient may have flu-like symptoms (elevated temperature, malaise), which are transient. If interferon alfa cannot stop the progression of the disease, the patient is prescribed **tenofovir or entecavir**. Both drugs can cause lactic acidosis, while tenofovir can still lead to impaired renal function, nephrogenic diabetes insipidus, or even acute renal failure. Tenofovir and entecavir inhibit hepatitis B viral DNA polymerase.

Until a few years ago, interferon-alpha 2a was used as the main drug for the treatment of chronic hepatitis C, but today it has been completely replaced by new drugs that act directly on the hepatitis C virus. There are several drugs that can be used, but they are classified in the group of **viral polymerase inhibitors** (the most used is **sofosbuvir**), in the group of **protease inhibitors** (the most used are **boceprevir and grazoprevir**) or in the group that inhibits the function of the **NS5A protein**, which is necessary for the functioning of the viral polymerases (the most used **ledipasvir**). The therapy is always a combination of two drugs with different mechanisms of action, whereby it must first be checked which of the 6 possible genotypes the patient is infected with, and whether the selected drugs work on that genotype. The therapy lasts **12 weeks**, during which time more than 90% of patients are permanently cured. Side effects of sofosbuvir are headache, nausea, depression, sometimes reduced number of leukocytes, while ledipasvir causes a feeling of fatigue and weakness. Boceprevir can cause anemia and leukopenia in a significant number of patients.

For the treatment of AIDS (acquired immunodeficiency syndrome), several groups of drugs are used that interfere with certain stages in the reproduction of the virus. The first group of **reverse transcriptase inhibitors** was discovered, which is divided into three subgroups: **nucleoside** (zidovudine, stavudine, lamivudine, emtricitabine), **nucleotide** (tenofovir) and **non-nucleoside** (nevirapine, efavirenz). These drugs have pronounced side effects on the bone marrow, which is observed as the appearance of leukopenia and/or anemia, can cause lactic acidosis and sometimes pancreatitis. **Viral protease** inhibitors are the next group of drugs for AIDS (ritonavir, saquinavir, indinavir, etc.) which is given in combination with the previous one, and side effects include lipodystrophy, liver damage, interactions with other drugs on cytochromes in the liver (usually they inhibit the metabolism of other drugs and increase their concentrations in the blood) and sometimes heart rhythm disorders. **Viral integrase** is inhibited by dolutegravir, whose side effects are liver damage and allergic reactions. Finally, the entry of the virus into human cells is inhibited by **maraviroc** (taken orally) and **enfuvirtide** (administered subcutaneously). Maraviroc can sometimes cause jaundice and liver damage, and enfuvirtide can cause an application site reaction, neuropathy, and a higher incidence of pneumonia.

We always treat AIDS with combination of at least 3 drugs. If a patient with AIDS comes to a general practitioner, it is most important that the doctor, when prescribing other drugs, checks the literature for interactions with AIDS drugs. It is also important to periodically (every 3 months) control the patient's blood count, creatinine, transaminases, bilirubin and glycemia because these drugs often have a toxic effect on the bone marrow and liver. AIDS patients are also prone to pneumonia and other bacterial infections, so they deserve antibiotics at the first signs of infection.

TREATMENT OF VIRAL INFECTIONS IN THE ORAL CAVITY

The most common causes of viral infections of the oral cavity are herpesviruses (DNA viruses) and papillomaviruses (DNA viruses). Of the herpesviruses (HV), the most important causative agents of the disease are:

• HV-1, which causes vesicular gingivostomatitis and recurrent lip ulcer;

• HV-2, which causes genital herpes, and when found in the oral cavity, causes changes like HV-1;

• HV-3, or herpes-zoster virus, which causes varicella (sheeppox);

• HV-4, or Epstein-Barr virus, which causes nasopharyngeal carcinoma and infectious mononucleosis;

• HV-5, or cytomegalovirus, which causes chronic inflammation of the salivary glands and systemic infection;

• HV-6, which infects CD-4 lymphocytes and causes Roseola infantum in young children;

In people with normal immunity, there is no point in treating infections with HV-1 and HV-2 by antiviral drugs, because they pass spontaneously. Patients should be given only analgesics and drugs that coat the exposed mucous membrane, thereby reducing irritation. Antiviral drugs are given systemically primarily in patients who are under immunosuppression, or for the treatment of changes that are very pronounced. They should also be given prophylactically to people who have frequent recurrences of herpes infection in the oral cavity (more than 6 times a year). Acyclovir is usually used first, and in more complicated cases, other drugs effective against herpesvirus.

In the treatment of HV-3 infection, famciclovir and valciclovir are more effective than acyclovir. In elderly people, short-term high doses of corticosteroids should be given after antiviral therapy or simultaneously with it, because this prevents the later appearance of neuralgia. If neuralgia does occur, it is treated with smaller doses of antiepileptics or antidepressants.

Infection with HV-5 virus is treated with systemic administration of ganciclovir or valganciclovir. Infection with HV-6 does not require the use of antiviral drugs.

There are over 100 types of papillomaviruses. Those in the oral cavity can cause the appearance of common warts (verrucae vulgares), thickening of the mucous membrane due to

epithelial hyperplasia (Heck's disease) or condyloma (condylomata accuminata). Papillomaviruses are also thought to increase the risk of oral cancer. These lesions can be treated with topical application of 1% cidofovir gel. If the lesions are larger and do not respond to cidofovir, they can be treated by injecting interferon alpha or bleomycin into the lesions themselves. In extremely widespread changes, patients take orally tretinoin, a derivative of vitamin A, which causes the changes to regress due to better differentiation of the infected cells.

TREATMENT OF AMOEBIASIS AND TRICHOMONIASIS

Amoebae cause inflammation of the colon in humans, accompanied by chronic diarrhea with blood and mucus. Amoebiasis is treated with the oral administration **of metronidazole,** which kills vegetative forms of amoeba, and with the use of **diloxanide-furoate**, which kills cystic forms of amoeba. Amoebae can be permanently cured only by using both drugs.

Trichomoniasis is a sexual infection caused by the protozoan Trichomonas vaginalis. It is treated with oral **metronidazole,** mandatory for both partners.

TREATMENT OF SCABIES AND HEAD LICE

Scabies is treated locally by applying 25% **benzyl benzoate** or 0.3% **lindane** (an organochlorine insecticide) to the entire skin (except the head). In case of head lice, apply 1% **lindane** or 1% **pyrethrin** to the scalp. Pyrethrin is less toxic and more effective than lindane. In addition to applying these insecticides to the hair, in order for the person to be fully cured, it is also necessary to mechanically remove the lice eggs ("nits") from the hair by persistent combing with a special, thick comb occasionally dipped in a 9% solution of acetic acid.

TREATMENT OF HELMINTHIASIS

In our region, there are several types of helminths that can parasitize the human body. Of the roundworms, the most common are **Enterobius vermicularis** (about 1 centimeter in size, lives in the intestines and lays eggs perianally), **Ascaris lumbricoides** (about 15 centimeters in size, lives in the intestines, if it multiplies, it can block the intestine), **Trichinella spiralis** (lives temporarily in the intestines, the larvae penetrate the intestinal wall and go to the muscles and other organs where they die), **Ankylostoma duodenale and Strongyloides stercoralis** (they live in the small intestine and feed on blood from the intestinal wall, so they lead to anemia). Among the flatworms, liver flukes (**Fasciola hepatica**) can be found in our country, and from the tapeworms, pork and beef tapeworms (**Tenia solium and Tenia saginata**, which live in the intestine). Finally, canine tapeworm larvae can penetrate the liver and other internal organs and there turn into cysts (**Echinococcus**).

Enterobius vermicularis and Ascaris lumbricoides are successfully treated with **mebendazole**, which is administered orally for a maximum of 3 days. When treating these worms, all members of the household should be treated. Ankylostoma duodenale and Strongyloides stercoralis are treated with **albendazole or thiabendazole**, while Trichinella spiralis and Echinococcus are treated with **albendazole** alone. **Praziquantel** is the drug of choice for tapeworms, while liver flukes are treated with **triclabendazole**. All benzimidazoles (mebendazole, thiabendazole, albendazole and triclabendazole) interfere with the formation of **microtubules** in parasite cells, but they differ in their affinity for binding to different microtubule structures, hence the differences in the spectrum of action. The most important side effects of benzimidazole are headache and liver cell damage. Praziquantel increases the permeability of parasite cell membranes **to calcium**, resulting in tapeworm paralysis, detachment from the intestinal wall, and elimination in the stool. Praziquantel exhibits only mild side effects: headache, loss of appetite, weakness. All the mentioned drugs are taken orally.

IMMUNOSUPPRESSANTS

Immunosuppressants are drugs that suppress the functioning of the immune system and thereby either prevent transplant rejection or inhibit autoimmune processes, where the immune system attacks its own cells. Immunosuppressants can be divided according to the part of the immune system on which they act.

Immunosuppressants that act on T lymphocytes

This group of immunosuppressants is divided into drugs that block signal 1 (primary interaction of T lymphocytes with antigen-presenting cells) or signal 2 (additional interaction between T lymphocytes and antigen-presenting cells that leads to complete activation of T lymphocytes). Signal 1 is blocked by **calcineurin inhibitors** (cyclosporine and tacrolimus) by preventing the initial activation of T-lymphocytes after interaction with an antigen-presenting cell. Calcineurin otherwise dephosphorylates the nuclear factor (NF) of activated T-cells, which then translocates from the cytoplasm to the nucleus, leading to gene transcription. Cyclosporine and tacrolimus have a common side effect - kidney damage due to the vasoconstrictor effect and direct toxic effect on the kidney tubule cells. Signal 2 is blocked by drugs that bind to CD80/86 proteins on antigen-presenting cells or to CD28 proteins on T lymphocytes (otherwise, the interaction of these two proteins is necessary for full T-lymphocyte activation to occur). **Abatacept and belatacept** are antibodies created by fusion of the Fc fragment of human antibodies and cytotoxic T lymphocyte-associated protein number 4 (CTLA4), which bind to CD80/86 and thus block the immune response.

Immunosuppressants that act on B lymphocytes

Immunosuppressants that act through B lymphocytes can affect the ability of these cells to create antibodies, but also their interactions with T lymphocytes, thus preventing the strengthening of the immune response. A number of drugs block the CD20 transmembrane protein on B lymphocytes, which normally regulates their entry into the division cycle and differentiation; blockade of CD20 protein is accompanied by a decrease in B lymphocyte function. CD20 receptor blockers include **rituximab** (a chimeric monoclonal antibody) and **ofatumumab** (a humanized monoclonal antibody), which are used in the treatment of several autoimmune diseases, e.g., nephritis. Monoclonal antibodies cause infusion reactions (temperature rise, hypotension, bronchospasm) and can lead to reactivation of some viral infections, e.g. hepatitis B.

Bortezomib, which inhibits proteasomes (intracellular structures that degrade damaged proteins in the cytoplasm), has proven to be particularly useful as an immunosuppressant. Since plasma cells are highly metabolically active, their functioning depends on the timely removal of dysfunctional and damaged proteins, so the administration of bortezomib can greatly affect the functioning of plasma cells and their ability to secrete antibodies. Adverse effects are cytopenias and peripheral neuropathy.

Immunosuppressants that act on cytokines

The oldest drugs that indiscriminately reduce the production and release of cytokines are corticosteroids. They inhibit the transcription factors NF-κβ and activator protein-1, as a result of which the synthesis of cytokine precursors is reduced, and the immune response as a whole is reduced. Corticosteroids reduce the secretion of cytokines and the number of T-lymphocytes, while they have no significant effect on B lymphocytes. Corticosteroids are very effective immunosuppressants, but they have many side effects.

Of the immunosuppressants with a selective effect on certain cytokines, the monoclonal antibody **basiliximab** (blocks the receptor for interleukin 2, which normally activates T lymphocytes; it is used to prevent acute rejection of kidney transplants) and the group of monoclonal antibodies that bind to tumor necrosis factor alpha (TNF- alpha) preventing its stimulating effect on the proliferation of T1 lymphocytes and synovial cells to produce collagenase and thus destroy cartilage and bone (**TNF-alpha inhibitors: infliximab, adalimumab, certolizumab**). **Etarnecept**, a chimeric protein consisting of the receptor for TNF-alpha and the Fc fragment of human antibodies, also binds to TNF-alpha. A common side effect of these drugs is a higher frequency of infection with intracellular pathogens (tuberculosis, cryptococcosis, coccidiomycosis). TNF-alpha inhibitors are mostly used in the treatment of rheumatic diseases.

Blockade of interleukin 6 has been shown to be very useful in rheumatoid arthritis, as it prevents its effect on the differentiation of CD8 T lymphocytes and B lymphocytes. **Tocilizumab** is a humanized monoclonal antibody that binds to interleukin 6 and prevents its action.

Polyclonal antibodies

Gamma-globulins for intravenous administration are preparations obtained from the plasma of a large number of donors. Since they represent a mixture of a large number of antibodies against the most diverse antigens, intravenous gamma-globulins bind many pro-inflammatory proteins and antigens, inhibit complement fixation in tissues and stimulate the release of some anti-inflammatory mediators. Adverse effects of intravenous gamma-globulins are acute kidney failure, infusion reaction and occurrence of thrombosis.

Antithymocyte globulin is a polyclonal preparation that contains antibodies against multiple antigens on T lymphocytes. When administered intravenously, it destroys a large

percentage of T lymphocytes, which makes it less likely that the transplant will be rejected. After its administration, infusion reactions often occur, sometimes pulmonary edema.

Immunosuppressants with an effect on several types of cells of the immune system

Alemtuzumab is a monoclonal antibody that binds to the CD52 protein on the membranes of both T and B lymphocytes, so it leads to a large decrease in the number of both types of lymphocytes, which means that both cellular and humoral immunity are weakened.

In lymphocytes of all types, there is a regulatory pathway called mTOR that is important for the transition of these cells from G1 to the S phase of the cell cycle. **Sirolimus and everolimus** block this pathway, so they have an immunosuppressive effect. Since the same pathway is found in other cells, e.g. endothelial, dendritic, etc., these drugs also have some antiproliferative and antitumor effects in certain tissues.

Antimetabolites interfere with DNA synthesis, so as lymphocytes belong to tissues whose cells divide rapidly, smaller doses of antimetabolites act somewhat selectively only on the immune system. **Azathioprine** is a pro-drug that is converted in the body into the antimetabolite **mercaptopurine**, while **mycophenolate mofetil** inhibits the synthesis of guanine nucleotides. The pyrimidine antagonist **leflunomide** inhibits dihydro-orotate dehydrogenase, an enzyme crucial for pyrimidine synthesis. A common side effect of antimetabolites is bone marrow suppression.

Finally, **cyclophosphamide**, a cytostatic from the group of alkylating agents, also acts as an immunosuppressant in small doses. It is used only in extremely severe forms of autoimmune diseases, because it can stop the process when the patient's life is threatened, but it has many side effects: hemorrhagic cystitis, the appearance of malignant tumors, permanent damage to reproductive cells in the gonads.

CYTOSTATICS

Cytostatics are drugs used to treat malignant diseases. Since, in addition to malignant cells, they also kill cells of healthy tissues that divide quickly (bone marrow, epithelium of the digestive tract, hair), in order to reduce damage to healthy tissues, cytostatics are applied in pulses – i.e., for just a few days a month, through 4 to 6 monthly

cycles. When a cytostatic is applied for 2 to 3 days, the patient does not receive therapy for the rest of the month to recover his bone marrow and epithelia. Before administering the next dose of cytostatics, it is necessary to check whether the patient's leukocyte, platelet and erythrocyte count has returned to a normal level. Cytostatics are very rarely used as monotherapy; they are usually given in a combination of two, three or even four drugs with different mechanisms of action and different side effects, in order to prevent the development of resistance of malignant cells and to avoid summation of toxicity on individual organs. Different combinations of cytostatics with specific recommendations for dosage and length of administration make up the so-called "therapeutic protocols" for certain types of malignant tumors. The main side effects of cytostatics are: leukopenia, thrombocytopenia, anemia (due to damage to the bone marrow), hair loss, nausea and vomiting, mouth ulcers, tendency to develop other malignant tumors and infections. Vomiting when using cytostatics is suppressed with drugs from the group of **5-HT3 blockers** (ondansterone, palonosetron, etc.) and the corticosteroid dexamethasone.

Cytostatics can be classified into several groups, according to their origin and mechanism of action. These are: (1) **alkylating agents**, which bind to DNA and interfere with its functioning (the most commonly used cyclophosphamide, chlorambucil, melphalan, etc.), (2) **antimetabolites**, which imitate folic acid, purine or pyrimidine bases and thus interfere with synthesis DNA, (3) **antitumor antibiotics**, which insert between two bases in DNA and thus interfere with its function, (4) **cytostatics of plant origin**, which interfere with the functioning of the division spindle, and (5) **hormones** and hormone receptor blockers which prevent the stimulatory effect of the female sex hormones on breast cancer and male sex hormones on prostate cancer.

Alkylating agents act on most tumors and on their cells in all phases of the cell cycle (whether the cell is quiescent or actively dividing); therefore, they are mostly used for the treatment of solid tumors (tumors that are seen as three-dimensional structures). These drugs bind to the nitrogen at the 7-position of guanine, creating unnatural bridges between parts of the DNA, which interfere with gene transcription.

Antimetabolites (methotrexate, which blocks the synthesis of methenyl-tetrahydrofolic acid, fluorouracil, which interferes with the incorporation of pyrimidine bases into DNA, and mercaptopurine, which interferes with the incorporation of purine bases) are primarily used for the treatment of leukemias and lymphomas, i.e. malignant diseases in which the reproduction of malignant cells is faster than in solid tumors. These drugs are dominated by side effects on the bone marrow, i.e. leukopenia, thrombocytopenia and anemia.

Antitumor antibiotics (doxorubicin and daunorubicin) are used in both solid and hematological malignancies. In addition to common side effects with other cytostatics,

antitumor antibiotics also have a specific toxic effect on the myocardium, so heart function must be carefully monitored during administration.

Cytostatics of plant origin include vincristine and vinblastine (which bind to microtubules and interfere with the formation of the dividing spindle in mitosis), as well as etoposide and taxols (paclitaxel and docetaxel), whose mechanism of action includes the blockade of topoisomerases, enzymes necessary to prepare DNA for replication. Cytostatics of plant origin have a wide range of antitumor effects, i.e,. they are used in a large number of tumors.

Hormonal therapy is very effective in tumors whose growth is influenced by sex hormones. Thus, malignant breast tumors that have estrogen receptors on their cells can be successfully treated for years with blockers of these receptors (**tamoxifen**) or drugs that reduce the production of estrogen in adipose tissue from androgens due to the blockade of the aromatase enzyme (**anastrozole**). A malignant prostate tumor in the metastatic phase can also be controlled for a long time by using testosterone receptor blockers (**flutamide)** or by using gonadotropin-releasing hormone analogs (**triptorelin, goserelin**) that prevent the release of pituitary hormones FSH and LH.

In addition to cytostatics, drugs with specific effects, which bind to receptors and/or enzymes crucial for the growth of malignant cells, have been used with increasing success for the treatment of malignant tumors in recent decades. A large group of **tyrosine kinase inhibitors** (imatinib, sunitinib, pazopanib, etc.) is active against many tumors, especially leukemias, kidney tumors or gastrointestinal stromal tumors, with side effects far milder than with classic cytostatics. Tyrosine kinase is an active part of many receptors and enzymes that regulate the growth and division of malignant cells. Several monoclonal antibodies (e.g., **pembrolizumab**) are now used as inhibitors of the interaction between programmed death receptors 1 (PD-1 receptors, which are found on lymphocytes) and the ligands of those receptors (PD-L1 ligands, which are found on tumor cells), thus **preventing the immunosuppressive action of tumors** and facilitating the human immune system to defend itself against tumors. Another name for inhibitors of the interaction of the PD-1 receptor and PD-L1 ligand is "**checkpoint inhibitors**" of the immune system; Pembrolizumab has been approved for use in malignant melanoma and lung cancer for several years.

ADVERSE EFFECTS OF DRUGS

Adverse drug reaction (ADR) is the body's response to a drug that is harmful and unplanned, and which occurs at doses normally used for prophylaxis, diagnosis or therapy of a disease, or changes in some physiological function. In addition to the aforementioned, unwanted effects include: unfavorable interactions between drugs, the absence of a therapeutic effect of the drug, and changes that follow the discontinuation of the drug to which the body has previously become accustomed.

There is no drug that does not have side effects; there are only drugs with more severe or mild side effects, depending on their ability to react with different tissues and organs. That is why side effects should always be considered when drugs are administered; then we will be able to predict and thus avoid some unwanted effects.

Adverse drug effects represent a major burden on the health care system. Studies have shown that about 6 percent of all hospital patients end up there because of adverse drug reactions. As many as 10 to 20 percent of hospital patients experience at least some unwanted effect of the drug while staying in the hospital. However, there is a great possibility that side effects can be avoided, if you think about them: even 50 percent of side effects are like that.

All side effects can be classified into three large groups:

- •A - ADR that can be predicted based on the mechanism of action of the drug (e.g., dry mouth when using tricyclic antidepressants, due to their antimuscarinic effect);
- B – bizarre ADR that are unpredictable, rare, do not depend on the dose, are usually serious (e.g., agranulocytosis with beta-lactam antibiotics);
- C - ADR that imitate diseases (e.g., a syndrome similar to systemic lupus erythematosus when using procainamide or hydralazine).

The frequency of side effects of a drug varies: some occur more often than others. In order to have an orientation, how likely it is that an unwanted effect of a certain drug will appear, they can be classified by frequency into:

- very common: occur in more than 10 percent of patients;
- common: occur in 1-10 percent of patients;
- they are not common: they occur in 0.1 - 1 percent of patients;
- rare: occur in 0.01 percent - 0.1 percent of patients, i
- very rare side effects: they occur in less than 0.01 percent of patients.

Of the unwanted effects, we are most concerned about the so-called serious side effects. These are side effects that lead to some of the following consequences:

- death
- hospitalization
- extension of hospitalization
- disability
- danger to life
- malignant disease or
- congenital anomalies.

For each drug that we give to a patient, we need to know the serious side effects that it can cause, to warn the patient about them and to familiarize him with the ways to prevent them (for example, patients who receive diuretics should not sunbathe, because it can cause occurrence of phototoxic or photoallergic reaction).

When we notice an unwanted phenomenon in a patient who is taking a medicine, we are not immediately sure that it was that medicine that caused the noticeable phenomenon. That's why we call such phenomena "adverse events" in the beginning, and we can call them "adverse effects" only when we determine the cause-and-effect relationship between the drug and the phenomenon. When determining the cause-and-effect relationship, we pay particular attention to the following elements:

- Challenge - The time interval from the administration of the drug to the occurrence of ADR? If the adverse event occurred during the administration of the drug, or soon after the cessation of administration, it is more likely a consequence of the administration of the drug than some other factor.
- Dechallenge - What happens after stopping the drug? If the adverse event recedes after stopping its use, it is probably a side effect.
- Rechallenge - What happens after re-administration of the drug? If after re-administration of the drug we observe an adverse event again, there is a very high probability that it was caused by it.
- Are there alternative causes of ADR? If there is no other explanation for the occurrence of an adverse event, the drug remains the most likely cause.
- Has such an adverse effect already been described? The experiences of others with the administration of a drug followed by an adverse event are always useful to us in determining causality.
- Is there a laboratory confirmation? For example, an increase in aminotransferases in the blood of a patient who developed nausea and vomiting during the administration of the drug significantly suggests that chemical hepatitis has occurred).

- Is there a suitable biological explanation for the occurrence of the unwanted effect of the drug, i.e. can we guess the mechanism of the side effect?

It is the duty of all healthcare workers to report any observed adverse event to our National Center for Adverse Drug Effects at the Agency for Medicines and Medical Devices of Serbia, on a special form that can be downloaded from the Agency's website. Therefore, only the suspicion that it is an unwanted effect is enough to fill out and send the application. For new drugs, all adverse effects are reported within the first 5 years from the moment they are registered in Serbia. For drugs that have been on the market for more than 5 years, only serious side effects and previously unknown side effects are reported. The National Center is obliged to anyone who reports an adverse event and seeks an explanation, to provide an assessment of the cause-and-effect relationship between the adverse event and the drug, with the help of its experts.

Regular reporting of all observed adverse events is important for the overall safety of drug administration in the country. It makes it possible to detect dangerous drugs, which cause many serious side effects, and to quickly ban their further use. Unfortunately, healthcare professionals rarely report adverse drug reactions, and it is estimated that the number of reported cases is only 1-10 percent of the actual number. In Serbia, that number is even smaller - only a few hundred applications per year. Why adverse drug effects are underreported is still unclear, but several reasons are hypothesized:

- complacency and the belief that only safe drugs are on the market;
- fear of being sued by the patient;
- feeling of guilt, because the drug caused the patient discomfort;
- desire to publicize side effects;
- not knowing how to apply;
- reluctance to report only suspicion, and
- lethargy.

BASIC PRINCIPLES OF POISONING TREATMENT

When a poisoned patient is brought to a doctor, resuscitation measures should be taken immediately, followed by measures to remove the poison and prevent its absorption. When we make sure that the patient is breathing and his heart is working, we should immediately remove the poison from the site of action.

If the poison got into the eye, it should be washed immediately with 2 to 3 l of plain water, which is injected into the eye using a syringe in individual portions of 2 to 3 ml.

If the poison is spilled on the skin, it should be washed immediately with as much water and soap as possible and the clothes should be removed.

If the poison has been swallowed, and no more than 4 to 6 hours have passed, it should be removed from the stomach. We do this by inducing vomiting, especially in children (a child's esophagus is several times more resistant than an adult's esophagus, so there is no risk of tearing due to too intense vomiting) or by washing the stomach. Vomiting must not be induced in: those poisoned by acids and bases, in unconscious patients, in the case of poisoning with oil or its derivatives, and in the case of poisoning with poisons that cause epileptic seizures. Gastric lavage should not be done in case of poisoning with acids and bases, in case of poisoning with oil and its derivatives, and in case of poisoning with poisons that cause an epileptic attack. In unconscious patients, gastric lavage can be performed if we have previously intubated the patient and protected the airway. After vomiting or gastric lavage, we give the patient oral activated charcoal (1 g/kg) and the laxative magnesium sulfate ("bitter salt", 15 g) with several glasses of water, in order to empty the intestines. The elimination of poison that has already entered the body can be accelerated by the use of Henle’s loop diuretics (forced diuresis), hemodialysis or hemoperfusion. The condition for applying these measures is that the poison does not have an excessively high molecular weight and that it is distributed only in the extracellular fluid (because then its concentration in the blood is higher, so it passes more quickly into the dialysis fluid or binds to the hemoperfusor). We use hemodialysis for poisons whose molecules are small (e.g., alcohol), and hemoprefusion for poisons with larger molecules.

For some poisonings, we can apply specific antidotes. These are substances that directly neutralize the poison or block its action. The most important antidotes are: (1) for poisoning with organophosphates (insecticides and battle poisons) - **atropine and pralidoxime**, (2) for poisoning with paracetamol - **acetylcysteine**, (3) for poisoning with benzodiazepines - **flumazenil**, (4) for poisoning with opioids - **naloxone**, (5) in carbon monoxide poisoning - **oxygen**, (6) in methanol and ethylene glycol poisoning - **ethanol or fomepizole**, (7) in heavy metal poisoning - chelates (substances that bind directly to heavy metals and thus prevent their binding to cells - eg dimercaprol), (8) in cardiotonic glycoside poisoning - **Fab fragments of antibodies**, and (9) in cyanide poisoning - **hydroxycobalamin (vitamin B12), sodium thiosulfate and sodium nitrate**.

Finally, many poisons cause methemoglobinemia, which we treat with **methylene blue**.

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