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# Clinical pharmacology for dentists

**Kyiv – 2023**

Approved by the Academic Council "Kiev International University"

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# Clinical pharmacology for dentists

Text book for dental students

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CLINICAL PHARMACOLOGY FOR DENTISTS

Textbook for dental students

**Foreword**

Traditionally, the study of clinical pharmacology (CP) has been considered the domain of internists - physicians, one of whose prerogatives is to prescribe drug therapy.

However, the development of medicine has shown that no matter what branch of medicine a medical specialist works in, he or she must be broad-minded, knowledgeable in fundamental disciplines and able to apply this knowledge in practice. QF, being to some extent an "applied" discipline, provides the practical application of pharmacology in the clinic and is therefore necessary in any area of medicine where medicinal products (MPPs) are used.

It is therefore necessary to study it not only for doctors in clinical specialties, but also for dentists, who are now faced with the need to prescribe medicines on a daily basis, and, of course, need training manuals aimed at them.

The textbook is divided into two sections: the first deals with general CF, covering the basics of pharmacokinetics, pharmacodynamics, and rational pharmacotherapy. It also includes information on the rules of clinical trials and the basics of evidence-based medicine. The second section deals with specific issues in clinical pharmacology with an emphasis on drugs used in dentistry. The second section is structured as follows: first, the indications for use in dentistry and the definition of the pharmacological group are presented, followed by a summary of basic pharmacology, indicating the generally accepted classification of the group, the most common chemical properties, mechanism of action and pharmacodynamic effects, features of pharmacokinetics,

The adverse effects, interactions and contraindications for use, as well as the features of clinical use in different categories of patients (children,

The chapter concludes with a description of the individual medications.) dentistry and control tests, the answers to which are given at the end of the book. The textbook also includes a list of literature recommended for further in-depth study. The authors hope, It is hoped that this textbook "Clinical Pharmacology for Dentists" will contribute to improving the teaching of clinical pharmacology in medical dental institutes.

# List of abbreviations and designations

A-B (blockade) - atrioventricular (blockade)

ADP - adenosine diphosphate AMP - adenosine monophosphate

ARV - antiretroviral drugs IV - intravenous

HAART - Highly Active Antiretroviral Therapy HIV - Human Immunodeficiency Virus

GABA receptor - subtype A receptor for gamma-aminobutyric acid (CNS inhibitory mediator)

GCS - Glucocorticosteroids DIC - disseminated intravascular coagulation GI - gastrointestinal tract

HRT - hormone replacement therapy TIA1 - plasminogen activator inhibitor TIA - coronary heart disease IP - HIV protease inhibitors CL - clinical pharmacology LP - drug

MD - medical and preventive treatment facility PM - medicinal product.

MAC - minimum alveolar concentration NRTI - nucleoside reverse transcriptase inhibitors of HIV

NNRTI - non-nucleoside reverse transcriptase inhibitors of HIV NR - adverse reaction TPR - total peripheral vascular resistance

PABA - para-aminobenzoic acid SAW - surfactants PG - prostaglandins RSV - rhinosynthetic virus

Mucosa - oral mucosa STH - somatotropic hormone.

TAF - platelet-aggregating factor TELA - pulmonary embolism COPD - chronic obstructive pulmonary disease.

CMV - cytomegalovirus CNS - central nervous system BP - respiratory rate

BHR - heart rate - craniocerebral trauma Key terms and concepts

# Introduction

Among the possibilities that modern dentistry has to provide effective and quality dental care, medicines occupy an important place.

The range of medications used in dentistry at present steadily increases. In the 70s, for example, dentists in Russia used about 100 drugs, and in the 90s - already more than 500. In this case, both the replacement of old drugs for new, more effective, and the expansion of the indications for use, and, The change in the approach to dental care has also been accompanied by the expansion of the indications for use and, consequently, the increase in the range of drugs used.

The change in approaches to the provision of therapeutic, orthopaedic and endodontic dentistry, orthopaedic and endodontic care and the inclusion of modern methods of anaesthesia contribute to the wider use and increase in the range of local anaesthetics, analgesics and antibiotics used. On the other hand, the increase in the educational level of the dentist, the emergence of new dental specialties and the expansion of responsibilities have led to the need to use groups of drugs not previously used in dentistry practice. All this requires a more in-depth study of the pharmacology in relation to the specific situation.

There are the following indications for the use of LPs in dentistry:

- ~ prevention and treatment of caries and non-carious dental hard tissue lesions;
- ~ treatment of pulpitis, periodontitis, periodontal disease, oral mucosa, treatment of infectious inflammatory diseases of the maxillofacial area;
- ~ treatment of other infectious diseases of the mouth and mouth.
- ~ facial area;
- ~ premedication and anaesthesia;
- ~ management of emergencies;
- ~ diagnosis of diseases of the oral cavity.

In his practice, the dentist must take into account that dental diseases can be combined with various general medical pathologies, as well as accompanied by their exacerbation. According to statistics, about a third of patients who come to the dentist have concomitant diseases, of which the most common are cardiovascular, endocrine and gastrointestinal diseases; and 12% of patients are elderly and elderly with polymorbid pathology (Bisyaev A.F. et al., 2002). In this case the dentist carries out treatment against the background of already

The dentist conducts treatment against a background of already conducted drug therapy, which increases the risk of unwanted drug interactions.

It should be taken into account that taking drugs of systemic action may be accompanied by the development of adverse effects, including in the oral cavity, and with local use of drugs can manifest their resorptive effect.

All this requires the dentist, as well as any other specialty, to know about the properties of the drugs used, their interactions, the particular effects on patients with different chronic diseases, different ages and anamnestic information. At the same time, the dentist must be able to use medicines both for the prevention and treatment of dental diseases and for the prevention of complications and relief of acute conditions in patients with concomitant pathology.

This means that the dentist is faced with the problems of optimal choice and the most rational use of drugs, and KF is the discipline, is the discipline that is designed to help solve these problems.

# SECTION 1 GENERAL ISSUES IN CLINICAL PHARMACOLOGY

## Chapter 1 Subject of Clinical Pharmacology

Clinical pharmacology is the science that deals with the interaction of medicines with the body of healthy and sick people and is concerned with the rational, safe and effective use of medicines.

The subject of the study is the drug-patient system, i.e. the efficacy and safety of medicinal products in clinical practice.

The aim of QF is to optimise pharmacotherapy for various physiological and pathological conditions.

The goal of QF has been defined by the World Health Organization (WHO) as improving the health of patients by improving the safety and efficacy of the use of medicines.

The range of problems addressed by QF includes:

~ development of rational effective and safe drug therapy regimens tailored to the specific clinical situation, their economic evaluation

~ clinical trials of new medicines and investigation of effects of known medicines in order to improve indications for their use

~ informing and educating doctors and students on rational use of medicines drags.

*Medicines* are dosage forms of medicines that are ready to be taken.

Medicinal products have several names:

~ chemical name

~ international nonproprietary name (INN), usually recommended by WHO and approved by official bodies, by which a drug is identified in various regulatory documents and diagnostic guidelines, prophylaxis and treatment

~ trade or brand names, which are the commercial property of the manufacturer.

Effectiveness of medicines is a characteristic of the extent to which medicines have a positive effect on the course of a disease; *quality of medicinal products* - compliance of medicinal products with the state quality standard for medicinal products.

There is no single classification of pharmaceuticals. They are divided into groups depending on the therapeutic purpose (painkillers, antivirals), pharmacological effect of (anticoagulants, bronchodilators), chemical structure (opioids, benzodiazepines), by nosological principle (caries remedies, gingivitis remedies). In clinical practice, a mixed classification is usually used, which makes drug selection more convenient. This "mixed" approach is also used in this textbook.

The main sections of QF are pharmacodynamics and pharmacokinetics. It also studies drug-food interactions and the undesirable effects of drugs. In recent years, pharmacogenetics, a branch of CF, has been developing rapidly. Pharmacoeconomics and pharmacoepidemiology have emerged from KF and gained independent importance.

# Chapter 2: Pharmacodynamics

*Pharmacodynamics* studies biological and therapeutic effects of drugs on the body, their mechanism of action. The pharmacodynamic properties define the group to which a drug belongs which the drug belongs and are crucial in selecting a drug for the treatment or relief of symptoms of a particular disease.

## 2.1 The mechanisms of action of the drugs.

The actions of drugs are determined by their ability to influence the general reactions of the body and the individual links of biologically important processes. This effect is mediated through controlling systems: receptors, enzymes, transport systems, specialized macromolecules, such as DNA. Some drugs interact with a number of controlling systems, causing many pharmacological effects, other drugs bind only to specialised cell components, modifying their function and that of the system they control. Biologically, they are more selective and have a specific structure, by making small changes to which the nature of their action can be significantly altered.

Several types of *mechanisms of action of drugs* can be distinguished.

1. *Action on specific receptors*. Most receptors are protein macromolecules that are selectively sensitive to specific chemical compounds. Drugs that directly stimulate or increase functional activity of a receptor are called agonists (stimulants), and drugs preventing interaction of endogenous and exogenous agonists with receptors are called antagonists (blockers). Some drugs that block a receptor can also partially stimulate it, i.e. they have both agonist and antagonist properties. They are called partial agonists. Their effects are dose-dependent. For example, nalorphine in normal doses acts as an opioid antagonist in relation to its depressant effect on the respiratory centre, but in higher doses can increase respiratory depression.

The receptor type of interaction also includes the effect of drugs when they bind to the cell genome (steroid hormones, vitamins A and D).

The speed and strength of drug binding to receptors is referred to by the term 'affinity'.

When receptor affinity is high, the desired effect is achieved at low drug concentrations. When the dose, and therefore the drug concentration, is increased, the drug binds to receptors to which it has a lower affinity, leading toIncreasing the number of pharmacological effects, decreasing the selectivity of the drug action.

The number of receptors in the body varies according to individual differences, age and different diseases. Drugs acting on the same receptors may have different affinity to them and more active ones displace less active receptors, which may lead to adverse effects of the drug, for example, development of hemorrhagic syndrome when concomitant use of indirect anticoagulants and non-steroidal anti-inflammatory drugs. The effect of a single drug application depends on the ratio of the number of receptors occupied to the total number of receptors and the retention time of the drug at the receptor.

The potency of a drug also depends on the speed and nature of the receptor changes: if they occur, increasing the dose does not increase the pharmacological effect any further. Some antagonists bind receptors irreversibly (e.g. some toxins). Normalisation of the response in these cases can only occur after the drug has been eliminated from the body and new receptors have been synthesised. Therefore, the effects of such drugs continue even after the drugs have been discontinued. The nature and strength of the drug/receptor interaction is manifested by the pharmacological response, which is due to the direct action of the drug, less often to changes in the conjugated system and only in isolated cases may be reflexive.

Depending on their sensitivity to natural mediators and antagonists, receptors are divided into cholinergic (acetylcholine-sensitive), adrenergic, histamine, dopamine, opioid, etc.

2. *Interaction with enzymes*. Drugs may have a structure similar to the natural substrate and compete with it for the enzyme, thus inhibiting it and blocking the formation of biologically active substances. For example, the covalent binding of acetylsalicylic acid to cyclooxygenase irreversibly inhibits the platelet enzyme, as it lacks the system that synthesises the new protein. Therefore, small doses of this drug have a persistent and pronounced anti-aggregation effect.

3. *Physico-chemical effect on cell membranes*. Certain drugs, e.g, agents for general anaesthesia and local anaesthesia alter transport of ions through cell membranes by altering the transmembrane electric potential, thus affecting nerve and muscle cell activity.

4. *Direct chemical interaction*. Drugs can interact directly with molecules and ions. For example, interaction between antacids and hydrochloric acid, the action of many antidotes for chemical poisoning.

**Types of drug action**

The action of drugs, depending on how they are administered, may be systemic (generalized) or local (generalized) or localized. The latter effect occurs when using ointments, creams, powders, rinses, applications. If the drug penetrates the blood and other body fluids, its pharmacological effect may appear anywhere in the body. This should be considered by dentists as the oral mucosa is an ideal site for absorption. The main effect of a medicine is the one that is used for therapeutic purposes in a given patient. Other pharmacological effects are called non-main effects - secondary effects. If they cause functional impairment, they are considered adverse effects (AEs) or adverse effects (AEs).

In various cases the same effect may be considered primary and secondary, e.g. anaesthetic and antiarrhythmic effect of lidocaine.

There is also a reflex effect, when the drug effect is mediated by physiological reactions of the nervous system and is associated with irritation of sensitive endings in the skin, mucous membranes or vascular walls.

Depending on the breadth of the spectrum of action, the drugs can be divided into those with specific and non-specific effects. The latter include those that have a wide range of pharmacological effects and affect different biological support systems. It is usually very difficult to identify and accurately assess their effects. These include vitamins, herbal adaptogens. As a rule, if a drug has low selectivity and acts on many tissues and organs, it may cause a greater number of adverse reactions.

If a drug affects the receptor apparatus of certain systems as an agonist or antagonist, its actions are considered specific. Their effects are independent of the organ location of the receptors and the pharmacological responses are varied. For example, atropine relaxes the musculature of the bronchi, the digestive tract and reduces salivary gland secretion.

A drug exhibits a high degree of selectivity, or selectivity, if it changes the activity of the system only in a particular part of it or in one organ.

The lower the dosage of a drug and the less firmly it binds to the receptor, the more selective its action is. However, the selectivity of a drug is dose-dependent and at higher doses it is lost.

Ideally, every physician dreams of having a drug that has a strictly defined application point in the body and has an absolutely selective effect that can be accurately foreseen, quantified and dosed, while the patient's condition is not worsened by the occurrence of undesirable effects of the drug. However, there is no drug that has an absolutely selective effect on a receptor, system or pathological process.

When developing new drugs, pharmacologists spend a lot of effort on increasing drug selectivity. There are two main ways to do this: targeted drug synthesis (rational drug design). In this case, a drug is synthesised based on information about the structure

of the receptor corresponding to it. This has only become possible in recent decades when many receptors have been isolated and their structure has been studied.

However, selectivity is not always biologically possible.For example, antitumour drugs act on rapidly dividing cells not only in the tumour but also in other tissues (bone marrow, intestinal epithelium, etc.), while drugs blocking beta-adrenoceptors act on them in both myocardium and bronchial musculature. Thus . modifying the structure of a drug does not always help to improve its selective action. selective action of a drug.

Selective transport of the drug to the area where it should act. This can be achieved by targeted administration of the drug to the area of action, e.g. using nebulisers to deliver beta-2-agonists to the bronchi during an asthma attack, or using special dosage forms (e.g. drug-antibody complex selective against tumour cells, liposomal forms of antibiotics).

The indications for use are based on the effect of the medicine on the body. Diseases and conditions in which the medicine may be dangerous,

determine the contraindications. There are absolute contraindications, in which the use of the drug is strictly forbidden, and relative contraindications, when it can be used if absolutely necessary and when the benefits of its use outweigh its harms.

## 2.2 Changes in the effects of medicines with long-term use

**Long-term use**

When medicines are used repeatedly, their effects may change.

Several types of these changes are distinguished:

- cumulation,
- sensitization,
- tolerance (addiction) and tachyphylaxis,
- withdrawal syndrome
- cravings and dependence (see Chapter 7).

*Cumulation* (Latin: cumulatio) is the accumulation in the body and summation of the effects of certain drugs when repeatedly administered. Cumulation is more common with drugs that have a long half-life and may lead to overdose with toxic effects. Cumulation can be prevented by reducing the dose, increasing the intervals between doses, or by interrupting treatment.

*Sensitization* (lat. sensibilis - hypersensitivity) - increased sensitivity of the animal or human organism or individual organs to exposure to any stimuli. It can be the result of either immunological rearrangement or non-allergic processes. In the first case, antibodies are formed against a drug that has allergenic properties (or that the body acquires them), which build up and react with the drug the next time it is administered. B this leads to the development of an allergic reaction. The sensitisation process

depends on the dose used and the permissible dose can also be minimal. It is important that cross-allergies exist, i.e. an allergic reaction can develop to drugs with a similar chemical structure and therefore with similar allergenic properties, e.g. sulphonamides and novocaine. Sensitisation that is not related to allergic reactions may be due to the sensitisation of tissue receptors to other drugs by some drugs. For example, hypersensitivity of the myocardium to adrenaline during fluorotonic anaesthesia, leads to cardiac arrhythmias when the latter is administered.

*Tolerance* (Latin: tolerantia) is a decrease in sensitivity to the drug used. The effect of the drug is lost, necessitating a higher dose to achieve the effect which had previously been achieved with a a lower dose. This condition may be due to reduced absorption or increased metabolism as a result of enzyme induction. The development of drug resistance may also be due to decreased receptor sensitivity or depletion of mechanisms involved in drug activation or mechanism of action. When antibacterial agents are used, the reduction in treatment efficacy may be due to the development of resistance of the pathogens and is referred to as resistance. Cross-tolerance between drugs of similar chemical structure is possible. Sometimes there is also natural tolerance due to hereditary factors. The rapid development of tolerance after one or more doses of a drug is called tachyphylaxis. Withdrawal syndrome is a condition that occurs when a drug is suddenly discontinued.

It includes two phenomena: an abrupt exacerbation of the symptoms of the disease for which it was prescribed ("ricochet") or a secondary loss of physiological function, inhibited by the drug used. There are a number of drugs that have a high potential for withdrawal and should be withdrawn gradually (e.g. glucocorticosteroids, psychotropic medications), allowing the patient to adapt to lower drug concentrations.

## 2.3 Medication dosing

The therapeutic as well as the toxic effects of the drug are highly dependent on the dose. This is indicated by the Latin letter D. Drug dosage is influenced by factors such as age, sex, body weight, physiological condition, co-existing conditions, drug interactions. The dosing regime (amount of drug administered and frequency of administration) allows individualisation of therapy according to the pharmacokinetic characteristics of the drug in a particular patient. A distinction is made between:

*single dose* - the amount of a drug per administration;

*daily dose* - quantity of medication taken during a day;

*ccal dosage* - quantity of medication taken during a whole course of treatment;

*average therapeutic dose* - drug dose most frequently used in therapeutic practice;

*loading dose* - when it is necessary to quickly build up high blood concentrations of a medication, the first dose (loading dose) is higher than the subsequent ones;

*maintenance dose* - the amount of medication needed to maintain therapeutic drug concentrations in blood;

*the highest single dose* - the amount of medication to be used when the therapeutic effect of the average single therapeutic dose is insufficient;

*therapeutic upper daily dose* - quantity of medication used when the therapeutic effect of the average daily therapeutic dose is insufficient;

*toxic dose* - quantity of medication causing toxic effects;

*lethal dose* - the amount of medication that causes death.

The efficacy and safety of the drug also depend on the dose. The next section of clinical pharmacology, pharmacokinetics, is concerned with determining the dose of a drug.

# Chapter 3 Pharmacokinetics

Pharmacokinetics is a section of KF concerned with the analysis of changes in drug concentrations in the human body and the mechanisms responsible for these changes, which allows the study of absorption, distribution, binding to blood proteins, biotransformation and excretion. Knowledge of pharmacokinetic parameters of drugs and patterns of their changes in a particular patient allows you to choose the optimal dosing regimen and achieve its maximum effect, maintain this effect for a necessary period of time and ensure minimal risk of undesirable effects.

The pharmacokinetic cycle consists of a series of phases considered sequentially, although in real time they run in parallel, only predominating at certain times.

## 3.1 Drug absorption

*Absorption* or *absorption* refers to the passage of a drug substance through biological membranes into the blood (lymphatic) system, which provides a resorptive (overall) action. Absorption is influenced by the absorption surface area, blood flow and state of microcirculation at the injection site, dosage form, lipid solubility of the drug.

Membrane crossing is accomplished by 5 mechanisms:

*Passive (simple) diffusion* - lipophilic low molecular weight compounds pass through biological membranes along a concentration gradient, which depends on the degree of lipophilicity of the substance.

This is the most important mechanism of drug penetration and distribution in body tissues. The drug penetrates the biological membrane passively at a rate proportional to the concentration difference on either side of the membrane. No energy is required in this process. If the drug is a weak acid, it will be in a non-ionised form in an acidic environment, which improves its penetration through the biological membranes and should be administered orally after meals, when the acidity of the

gastric juice is at its highest. If it has weak basic properties, however, it is better administered before meals (1-1.5 hours) or 1-2 hours after meals when the acidity of the gastric juice is lowest.

*Filtration (convectional transport)* is the passage of drug molecules through the pores of membranes, which are small in size due to small pore size (up to 1 nm on average); apart from the size of molecules, filtration depends on their hydrophilicity, dissociation ability, ratio of particle charge to pore charge, as well as hydrostatic, osmotic and oncotic pressures; water, some ions and small hydrophilic molecules are absorbed this way;

*Passive diffusion* and, to a lesser extent, filtration serve as the main mechanisms of absorption in the oral cavity, stomach, colon, rectum and from the skin surface.

*Active transport* is via the transport systems of cell membranes (carrier molecules), requires energy and can run against the concentration gradient.

This mechanism is characterized by selectivity, competition of different substances for one carrier and "saturation". The latter lies in the inability to exceed a certain rate of the process, which is limited by the amount of carrier and does not increase with a further increase in the dose of the absorbed substance. In this way, hydrophilic polar molecules, a number of inorganic ions, sugars amino acids etc. In children and elderly people this way of drug penetration functions poorly.

*Facilitated transport* is similar to active transport. It can go against the concentration gradient, but is not accompanied by energy consumption.

The transport systems of this mechanism are strictly specific for each substance (for example for vitamin B12).

*Pinocytosis* is similar to phagocytosis: the uptake of the drug substance results from the invagination of the cell membrane to form vesicles that migrate along the cytoplasm to the opposite wall and empty out. In this way, drugs of polypeptide structure and large molecular weight enter the cells.

Of all the routes of drug administration used, the absorption mechanism is absent only in intravascular routes.

## 3.2 Main routes of administration

The main routes of drug administration can be divided into *enteral* and *parenteral.*

A. *Enteral* administration is the administration of a medicine through the digestive tract.

1.Most medications are given by mouth (per os, ingestion) due to the ease of use of this route. Absorption is most often in the proximal small intestine. This process is affected by the rate of gastric evacuation and the activity of peristalsis (if the evacuation

is slowed or the passage through the intestine is accelerated, absorption is reduced). Retarded dosage forms (slow-release forms) are absorbed in the colon.

2.Sublingually or buccally, medicines are used to increase the speed of achieving maximum plasma concentration (TCmax) and to eliminate the effect of first passage through the liver (see below). This is due to the abundant vascularisation of the SOPP and the fact that blood from the oral vessels enters the systemic bloodstream, bypassing the liver. The advantages of this route also include that the drug is not affected by gastric hydrochloric acid and gastrointestinal motility. Absorption is easily interrupted by spitting out the dosage form.

In this route of administration, the drug interacts with the oral environment. Its main component is saliva, which is a mixture of salivary gland secretion, oral mucosal glands and gingival fluid. Saliva is mildly acidic due to its buffer systems (pH averages 6.8). If the saliva reaction is more acidic, the active ingredient of the drug may be destroyed and the effect of the drug is reduced. Normally, 1.0-1.25 litres of saliva are produced per day saliva, or an average of 2.2 ml/min. Saliva secretion depends on the physiological condition (e.g. it increases when stimulated by food, and decreases when the sympathetic-adrenal system is activated as in fear or pain), age, general and dental pathology. Increased salivation promotes swallowing, which negates the benefits of this route of administration, while decreased salivation prevents dissolution and absorption of the drug. Disadvantages of this route also include discomfort with frequent and regular use, irritation of the oral mucosa and the development of drug-induced stomatitis. At the same time, special prolonged buccal dosage forms have been created.

The active substance is combined with a special base that gradually dissolves under the action of saliva, ensuring a prolonged and uniform delivery of the drug into the systemic bloodstream.

3. Rectally is administered when it is necessary to avoid direct irritation of the drug on the gastric mucosa or in children if the drug has an unpleasant taste.

The mucosa of the rectum does not contain enzymes that can break down drugs.

It has an abundant blood supply and a well-developed lymphatic system.

The outflow of blood from the lower parts of the intestine is bypassed by the liver. Medicines are easily absorbed and are not subject to the effects of first passage through the liver. At the same time there may be difficulties in dosing the drug as it is absorbed through the upper parts of the rectum and enters the portal vein system and the liver.

In addition, the drug may have an irritant effect on the rectal mucosa and in children and older age groups there may be difficulties in retaining the drug in the colon.

4. Drugs are administered into any part of the intestinal tube by means of probes or through fistulas, rarely and exclusively in surgical, intensive care or psychiatric practice (in the absence of parenteral forms).

B. *Parenteral* administration is the administration of a drug to obtain a resorptive effect, bypassing the digestive tract. These routes are used for drugs with low absorption or high liver-first-pass effect and strong irritant effect on gastrointestinal mucosa.

1. *Intravascular* administration of drugs varies in meaning and effectiveness depending on the vessel used. Intravenous administration is usually aimed at obtaining a rapid and pronounced effect. The intra-arterial route is rarely used and is mainly used to create a high concentration of the drug in a particular region.

Endolymphatic techniques have also been developed to produce localised high concentrations. The intravascular routes provide the most precise dosage of the drug and its complete entry into the systemic bloodstream (especially intravenous).

Rapidly excreted drugs are administered by intravenous drip infusions, which allows a stable concentration in the blood to be maintained. At the same time, there is a high risk of overdose, as well as the risk of thrombosis and thrombophlebitis and infection of the vascular catheter.

2. *Intramuscular and subcutaneous* administration, although compared to oral administration, allows for higher Tmax and faster attainment, certain limitations of these routes are related to the absorption mechanism present here. When regional blood flow and microcirculation are impaired or whensystemic microcirculatory disorders seen in shock, stress (in particular, absorption is delayed and the effect is lost, and repeated injections may lead to drug cumulation and overdose. Intramuscular injection is fraught with the development of postinjection infiltrates with possible infection and the development of purulent complications. Repeated subcutaneous injections of insulin cause atrophy of adipose tissue, impaired absorption of the drug.

3. *Inhalation* is intended for gaseous substances and volatile liquids. The drugs are rapidly absorbed and eliminated, allowing the concentration to be controlled and the effect of the drug to be monitored. This method of drug administration is primarily used in anaesthesiology. Often this route includes the administration of aerosolised dosage forms designed to produce local effects such as bronchodilation in patients with COPD. The name of the devices by which these drugs are administered also contributes to this interpretation "metered-dose inhalers". However, since in these cases the highest concentrations,

However, as in these cases the highest concentrations giving therapeutic effect are in the bronchial tissue, and absorption into the systemic circulation is minimal and determines only undesirable effects, it is more reasonable to consider inhalation of aerosols as a local treatment option.

4. *Transdermal* administration is usually used for long-lasting effects. In this case, special systems in the form of ointments or patches are used.

The release of the drug is gradual. This ensures a uniform transdermal absorption of the drug and allows a constant concentration of the drug in the blood to be maintained. Nitrates, fentanyl (for long-term pain relief in cancer patients) can be administered in this way. In children, especially during the first years of life, the skin

has a thin horny layer and absorption is just as easy, as with ingestion or when the skin is broken, so great caution should be exercised when using this route in children.

5. *Intranasal* administration, although commonly referred to as the parenteral route, is essentially intermediate between parenteral and local administration.

The nasal submucosa has a direct connection to the subarachnoid space of the olfactory zone of the brain, where the drug is delivered from the nasal cavity. Lipophilic substances are well absorbed in this route of administration. It is used for drugs acting on the CNS (in anaesthesia, premedication, migraine treatment) when obtaining a systemic concentration of the drug in the blood is not the goal.

6. *Local application of drugs to skin and mucous membranes*, in cavities, cerebrospinal fluid aims at maximum local concentrations with minimum drug absorption. This allows a pronounced therapeutic effect of the drug in the desired area and minimizes systemic undesirable effects. However, it is not possible to completely prevent systemic adverse effects due to the presence of some degree of drug absorption and the development of resorptive action. Topical application of drugs is widely used in dentistry for the treatment of oral mucosa and dental hard tissue. Dentists are therefore the ones most often confronted with the resorptive effects of drugs when they are applied topically, which is due to the structure of the oral cavity and its blood supply.

The absorption process can be characterised by the completeness and speed of absorption:

- ~ absorption completeness is the fraction of the dose absorbed into the blood (in %);
- ~ absorption rate is represented by 3 values
- ~ absorption rate constant ($C_a$),
- ~ time to maximum concentration ($T_{Cmax}$),
- ~ half-absorption period ($T_{1/2a}$) - time of receipt into the blood from the point of administration of half of the dose;
- ~ maximum concentration ($C_{max}$) - the highest concentration of a medicine in the systemic bloodstream, which depends primarily on completeness of absorption, but is also affected by the speed of absorption.
- ~ its value is also influenced by the speed of absorption and even the activity of the distribution process.

Absorption rate and completeness of absorption are independent of each other and may change in different ways for the same drug under the influence of the same factor. Presystemic elimination

When the drug is taken orally, apart from the biological membranes standing in the way from the intestinal lumen into the bloodstream, there is another factor limiting the drug's entry into the systemic bloodstream - hepatic metabolism. The drug substance, During entry through the portal vein from the gastrointestinal tract into the liver, the drug may be enzymatically degraded, so that only part (sometimes a small

part) of the administered dose reaches the systemic bloodstream. This phenomenon is referred to as the "first pass effect". first passage through the liver". For example, some drugs, while highly absorbed, enter the systemic bloodstream in very small amounts that have no therapeutic effect. This effect is characteristic of drugs that are rapidly metabolised (see biotransformation phase) and, if significant, precludes ingestion of the drug in (eg antiarrhythmics such as lidocaine). In other cases it can be corrected by increasing the dose, which is much higher than the intravenous route (verapamil, morphine, propranolol). The example of nitroglycerin is very demonstrative in this regard. The first pass-through effect in this drug reaches 85-97% of the dose, which explains the need to bypass the liver (sublingually or intravenously) and makes the often-used oral administration of "Votcal drops" (a solution of nitroglycerin in menthol).

The part of the administered dose that has reached the systemic bloodstream is the most important characteristic of the drug. The latter is referred to as 'bioavailability' and is defined by the WHO as the degree and speed with which a substance or its active ingredient is delivered from the dosage form into the systemic bloodstream. When administered intravenously, bioavailability is taken as 100%. When administered orally, it depends on a number of factors: resistance of the drug to the action of gastric hydrochloric acid, the activity of the drug in being broken down by enzymes in the lumen and intestinal wall the severity of the effect of first passage through the liver, i.e. the losses due to presystemic elimination.

Presystemic elimination depends not only on the drug, but also on a number of factors in the patient's body and the conditions of drug administration. Presystemic elimination is influenced by interactions with food and other medicinal products (see section 9), the rate of gastric evacuation, intestinal motor function, hepatic function and the state of the portal circulation. If liver function is impaired (in cirrhosis) or if a system of anastomoses between the portal vein and the vena cava (in portal hypertension) develops, the drug enters the systemic bloodstream, bypassing the liver. This reduces the effect of first passage through the liver, which may lead to drug overdose in spite of the therapeutic dose. In addition to the factors listed above, bioavailability is also influenced by the technology used to prepare the dosage form. Therefore, the bioavailability of the same active substance in different dosage forms or in preparations of different manufacturers may vary widely. However, such variations make efficient and safe dosing of medicines very difficult. Therefore, a bioavailability study of a new medicine in comparison with a reference medicine should be carried out before the registration of the medicine. The result is information on comparative bioavailability or bioequivalence.

## 3.3 Protein binding and distribution

Binding to blood proteins. Many of the drugs have a pronounced physico-chemical affinity for macromolecules, whereby, once in the blood or lymph, they bind to proteins and are present in the blood as two fractions: free and bound. Most drugs (salicylates, penicillins, sulphonamides and many others) bind to the main serum protein, albumin. To a lesser extent globulins, acidic alpha 1-glycoprotein and lipoproteins take part in this process, formamen. Some drugs bind to more than one structure at the same time.

Only the free, unbound fraction of the drug is pharmacologically active. Only it is able to penetrate through cell membranes, influence specific targets, undergo transformations by enzymes or be excreted from the body.

The drug-protein bond is rather fragile and the formation and disintegration of the "formation" and disintegration of the drug-protein complex occurs rapidly. Due to this fact, free and bound fractions are in equilibrium: in bound form, the drug circulates in the blood until the concentration of free fraction decreases, after which it is released, thus ensuring the stability of the plasma concentration. In other words, Once bound to blood proteins, the drug forms a depot. Protein binding becomes clinically relevant if it exceeds 80-90%. Thus, a decrease of the bound fraction of the drug from 98% to 96% can increase the free fraction from 2% to 4%, i.e. by 2 times, which is fraught with overdose. This can occur in various physiological and pathological conditions in which the amount of protein in blood decreases (e.g. neonates and especially premature infants, the elderly, emaciated patients, patients with impaired protein-synthetic function). Bound fraction decreases in chronic renal failure, chronic liver disease, sepsis, burns, protein starvation, not only due to hypoalbuminemia, but also due to the accumulation of metabolic products competing with the drug for protein.

Under pathological conditions changes in the value of the bound fraction can proceed in both directions. For example, in the antiarrhythmic drug quinidine, this index, Normal value is 87-92%, but in congestive heart failure this falls to 82% and increases to 96% in chronic respiratory failure. In myocardial infarction there is an accumulation of 1-acid glycoprotein, which contributes to increased binding of lidocaine, quinidine etc. Increased protein levels in blood, e.g. in cancer, may reduce the free drug fraction and therefore its effect will be reduced.

*Distribution in the body.* During this phase of the pharmacokinetic cycle the drug is distributed by blood throughout the body, penetrates into interstitial spaces, reaches the cells and accumulates in different tissues and organs. As a result of distribution, the drug reaches its target, binds with it and takes effect.

The distribution process continues until the speed of the drug in the tissue compares with the speed of its return from the tissue into the bloodstream. When these

velocities are equal, there is a state considered steady state, and concentration of the substance in the blood at this time is called equilibrium (Css).

The distribution of drugs in the body is never uniform, which depends on a number of physiological (pathophysiological) and pharmacological factors.

Among the properties of the drug that determine the nature of distribution, one can distinguish factors that determine the absorption capacity of the substance (overcoming biological barriers during distribution occurs according to the same laws as during absorption), affinity (affinity) to individual tissues (which determines the preferential accumulation of the drug), as well as binding to blood proteins. Hydrophilic substances have a low volume of distribution (see below), lipophilic substances have a high volume of distribution. The distribution can vary considerably depending on a number of characteristics of the body itself:

- ~ *the intensity* of regional blood flow under physiological conditions (the heart, liver, kidneys and endocrine glands are most actively supplied with blood);
- ~ *membrane permeability* and associated barriers (eg, membrane permeability (e.g. blood-brain barrier, placental barrier) for this substance under normal and abnormal conditions (see below);
- ~ *haemodynamic* and microcirculatory disturbances due to stress, shock and chronic cardiac insufficiency, which cause a decrease in blood flow of organs that are intensively supplied with blood (inhibition of inactivation of the drug in hepatic and urinary excretion is inhibited;)
- ~ *presence of congestive and inflammatory effusions in the cavities*, in which hydrophilic drugs can accumulate).

*The blood-brain barrier* is a mechanism by which the exchange of substances between the systemic bloodstream and the cerebrospinal fluid is highly selective. The endothelial cells of the cerebral capillaries are closely adjacent to one another and do not have spaces through which water-soluble drugs can penetrate into the cerebrospinal fluid, which determines this selectivity. At the same time, fat-soluble agents easily penetrate the blood-brain barrier.

In infective inflammation of the cerebral membranes, the blood-brain barrier permeability is also increased for water-soluble substances. However, as the concentration of drugs in the cerebrospinal fluid decreases rapidly (due to the fact that approximately one tenth of its volume is renewed within an hour, i.e. the drug is practically washed out), in this case it is also relevant to administer drugs directly into the subarachnoid space (intrathecally).

There are a number of characteristics to describe the distribution process, the most important of which are:

*distribution volume (apparent distribution volume)* is the hypothetical volume of fluid required to evenly distribute the entire amount of a drug at a concentration equal to its concentration in blood plasma (usually calculated as specific distribution volume per unit body weight); it reflects the degree of tissue uptake of the drug from blood plasma and relates the amount of drug in the body to its concentration in blood;

*the equilibrium (steady-state) concentration ($C_s$)* - is established in blood when the drug enters the body at a rate equal to its elimination rate, which can be achieved either by constant intravenous infusion or by administering the same dose at equal time intervals; if saturation doses are not used, $C_s$ is usually reached after 5-7 *semi-elimination periods* (see below); the lowest and highest drug concentrations at equal doses occur when the drug is given at certain intervals.

The lowest and highest concentrations at intervals of the same dose are considered to be the lowest and highest concentrations for low therapeutic latency (see below).

## 3.4 Biotransformation of drugs

When a drug is introduced into the body, processes are involved to break it down and excrete it from the body. Some water soluble drugs are excreted unchanged by the kidneys, others are affected by enzymes.

*Biotransformation (metabolism)* is a universal concept reflecting the chemical changes to which xenobiotics (foreign substances, including drugs) undergo in the body. The basic biological idea of biotransformation is to free the organism from the xenobiotic either through its utilization as an energy or plastic substrate, or by converting it into a form suitable for excretion. The relevant biochemical processes could therefore be regarded as a detoxification system, but such a view would be too simplistic.

*Firstly*, the toxicity of many xenobiotics is not due to the substance itself, but products of its biotransformation. This is also true of drugs. For example, the toxicity of lidocaine is determined by the formation of xylidide monoethylglycine during its biotransformation.

*Secondly*, a large number of drugs have active derivatives (metabolites), pharmacological activity of which is comparable or significantly higher than that of the original substance. For example, the activity of 4-hydroxy-propranololol, formed in the liver during first passage, is comparable to that of propranolol itself (anapriline, Obzidan); however, as the former has a shorter half-life (see below), different routes of administration result in different efficacies. In the example of the ACE inhibitor enalapril (renitec, enap), an increase in the activity of the pharmacological substance during biotransformation can be demonstrated, as its metabolite enalapril formed during

hydrolysis is 10 times more active than the original substance. In some cases, some drugs can be transformed into substances used as other drugs: e.g, codeine can be transformed into morphine or theophylline (in newborns) into caffeine.

*Thirdly*, there are a number of drugs which, while not pharmacologically active themselves, are transport agents of sorts. They are metabolized to pharmacologically active substances only after absorption and passage through the liver, e.g. the mucolytic bromhexin, or when ingested, e.g, the antiviral drug acyclovir. Such drugs are called prodrugs. Over time, it is sometimes possible to dispense with them by moving directly to the active ingredient: instead of the currently unused phenacetin ("prodrug"), its active derivative, paracetamol, is widely used.

Drugs are biotransformed in many organs. In descending order of importance, the organs and tissues involved in biotransformation can be arranged as follows: liver, stomach, intestines, kidneys, lungs, skin, brain. B The adrenal glands, smooth and striated muscles, vascular endothelium, blood, etc. may also be involved in this process.

*Two stages (two phases)* are distinguished in biotransformation reactions, each of which may be of independent importance.

In the first phase, the drug undergoes oxidation, reduction or hydrolysis.

A key role in this phase is played by the cytochrome P450 isoenzyme system, the main oxidizing system of the body, associated with the endoplasmic reticulum (endoplasmic or microsomal system). Liver and intestinal cells are particularly rich in enzymes of the cytochrome P450 system.

The most important properties of this system are:

*The ability* to biotransform almost all known chemical compounds;

*The ability* to bind molecular oxygen;

*High inductivity* (increase in enzyme activity under the influence of external factors).

Selective induction of certain isoenzymes and more or less non-selective induction are possible. The latter can occur under the influence of alcohol and tobacco-smoke ingredients, which can significantly reduce the efficacy of many drugs in people with so-called bad habits

It is important to emphasize not only the induction but also the inhibition of enzymes in this system (e.g. by acetic aldehyde, which is formed during ethanol reduction under the influence of alcohol dehydrogenase).

Although, as stated, the ultimate goal of biotransformation is "detoxification', epoxides and nitrogen-containing oxides can be formed from drugs that can react with proteins, damaging them and making them foreign to the body. This triggers an immune response and an autoaggression process. By damaging cell membranes, disrupting nucleic acid synthesis, epoxides, nitrogen-containing oxides and some other metabolites cause the processes of carcinogenesis, mutagenesis or teratogenesis. Examples of such potentially dangerous drugs include diphenhydramine (dimedrol) and trimethoprim (part of the co-trimoxazole combination drug biseptol, bactrim, etc.).

The second stage is the completion of detoxification. As a result of the formation of conjugates with residues of inorganic and organic acids, including amino acids (sulphuric, acetic, glucuronic, glutamine, glycine, glutathione) or methyl groups, the drugs almost completely lose their pharmacological activity and, becoming water soluble, are eliminated with urine or bile. It should be particularly emphasized that when each of the phases acts as an independent biotransforming system (e.g., oxidation of alcohol to carbon dioxide and water or acetylation of sulfonamides), high activity of one of them is usually combined with low activity of the other (which is genetically determined). For example, a very high percentage of "fast acetylators" among indigenous northern peoples is combined with a low capacity for oxidation of xenobiotics and poor tolerance of alcohol.

The biochemical processes of both stages I and II depend on the functional state of many body systems: the nature of tissue oxygenation, the state of hepatic blood flow (its reduction can lead to slower biotransformation), the protein and synthetic function in general and the activity of enzyme synthesis in particular, etc.

Since the activity of protein and enzyme synthesis changes with age, a decrease in biotransformation of xenobiotics is observed in older age groups (which requires special caution when dosing them). Significant features of drug biotransformation are observed at different periods of maturation in children (with which the known limitations of certain drugs in paediatrics and paediatric doses are associated). For example, the lack of maturity of enzyme systems in neonates and infants results in fat-soluble drugs remaining pharmacologically active longer.

Many drugs undergo several reactions of each phase at the same time.

This duplication ensures high reliability of the system as a whole. However, the end products of biotransformation may differ when individual body systems are altered, e.g. in children of different ages.

Since biotransformation is most active in the liver, all drugs can be divided into those with high and low hepatic clearance (see below).

## 3.5 Drug excretion

Drugs can be excreted from the body with any fluids (urine, saliva, sweat, bile, breast milk, etc.) and volatile ones (gaseous and volatile anaesthetic fluids, essential oils such as camphor) - also with exhaled air. In practice, however, for the vast majority of drugs the kidneys and the gastrointestinal tract are clinically important as a route of excretion. Depending on their hydrophilicity or lipophilicity, their ability to be filtered, secreted and reabsorbed in the kidneys, their ability to be secreted into the bile and their absorption in the gut, medicines and their derivatives (if biotransformed) are excreted by one of these two main routes.

Excretion of drugs with milk is important in breastfeeding mothers and with saliva is important in the development of adverse oral effects.

Renal excretion of drugs and their metabolites includes filtration, secretion and tubular reabsorption.

Ductal filtration is a passive process whose rate depends on the concentration of the substance in the blood, its molecular weight and charge: substances with a high molecular weight or bound to blood proteins are hardly filtered.

Secretion in the renal tubules is an active process in which special transport systems are involved, transporting molecules from the plasma into the tubular fluid and not depending on the binding of the drug to blood proteins. The same transport systems may be involved in the excretion of different substances, which may create competition in the excretion of the latter (see chapter Drug interactions).

The tubular reabsorption of some substances (glucose, amino acids, ionised compounds) is active, while that of others (fat-soluble) is passive. Therefore, lipophilic molecules, once in the primary urine, are actively reabsorbed by simple diffusion and cannot be excreted this way.

Thus, hydrophilic ionised and polar molecules (starting substances and biotransformation products) are usually excreted by the kidneys. Since their degree of ionisation varies at different pH values, the renal excretion of drugs can be significantly influenced by the pH of the urine, which itself can be influenced by other drugs (see chapter "Drug interactions") or food. For example, acetylsalicylic acid, by dissolving in the alkaline environment that is created by the consumption of certain foods or the taking of certain medicines, becomes less soluble and its reabsorption decreases and its excretion increases. This effect is used in overdoses of this and similar drugs.

The second most important route of excretion is by the GI tract. The entire volume of the drug excreted by this route consists of several fractions:

- the portion of the dose that has not been absorbed into the GI tract (unchanged);
- unchanged substance and, more often, its derivatives that are secreted by the liver into the bile and excreted with the bile into the intestinal lumen;
- part of the dose that has been biotransformed in the stomach and intestine (as derivatives);
- unchanged substance or its derivatives excreted by the stomach or intestinal wall.

The first two fractions are of primary clinical importance, as they determine the greatest volume of drug excretion by this route. Bile excretion is not limited by the high molecular weight and protein binding. However, this route also has its limitations. In particular, the substance excreted with the bile into the intestinal lumen can be re-absorbed. This applies especially to glucuronic acid conjugates, which can be hydrolysed by the intestinal flora, whereby the originally released substance can be re-

absorbed and partly reabsorbed into the systemic blood stream and partly reexcreted by the liver. This phenomenon is called *enterohepatic circulation* or *hepatic recirculation*. Reabsorption of the substance excreted into the intestinal lumen leads to new peaks of drug concentration in the blood and contributes to a longer maintenance of high concentrations, which plays an important role in intoxication and often requires administration of enterosorbents regardless of the route of administration of the drug.

Elimination is generally characterised by an index called *clearance* ($Cl_{gen}$), which is the volume of blood (plasma, serum) that is completely eliminated from a given substance per unit time (l/hour, ml/min.). In practice, this indicator is important for the calculation of maintenance doses.

This indicator is important for the calculation of maintenance doses (D-sustained) of difficult to administer drugs such as digoxy or theophylline. The maintenance dose should equalise the excretion rate and the rate of drug intake, i.e. turn the achieved concentration into the equilibrium concentration (CSS):

$$D_{supplemental} = C_{SS} * Cl_{gen}$$

For most drugs, total clearance is a constant and concentration-independent value. However, for some, e.g. phenytoin (diphenin), acetylsalicylic acid (aspirin), clearance is not constant and elimination is a saturable, dose- and concentration-dependent process.

Total clearance is made up of hepatic and renal clearances of the drug. Organ clearance generally depends either on the rate of blood flow through that organ or the concentration of the substance in the blood, or both. It depends on the biotransformation activity of the substance, the available supply of the enzymes involved, the extent to which the drug binds to proteins. In any case, when prescribing a drug that is excreted by any route, it is necessary to assess, at least at a qualitative level, the blood flow in the organ, the blood supply to kidneys and liver in case of shock, congestive heart failure, hepatic circulation in alcoholic cirrhosis, etc.

Endogenous creatinine clearance is used to assess renal function. Normal clearance is 80-120 ml/min. It can be calculated using appropriate formulas based on serum creatinine and daily urinary creatinine excretion, or by using special nomograms depending on the serum creatinine level, body weight and height of the patient. According to the creatinine clearance value, the physician has to adjust the dosage and the frequency of drug administration in renal failure.

One of the most important pharmacokinetic parameters is the s*emi elimination period* - $T_{1/2}$ (elimination period, half life period) - the time it takes for the plasma concentration of the drug to drop below the threshold of elimination of drug concentration in blood plasma by 50%. It expresses the relationship between the volume

of distribution and clearance. The elimination half-life is used to determine the time during which during which an equilibrium concentration of a medicine in plasma is reached with regular administration (see above).

## 3.6 "Original" and "generic" medicines, bioequivalence

In any drug, a distinction can be made between the inactive ingredients used to make the corresponding dosage form and the active ingredient itself. The latter has an INN and because it may be present in a whole family of the same drugs can be considered the generic name of all these drugs.

Among the plethora of drugs with the same generic name, it is possible to distinguish between originals and generics.

In accordance with the Federal Law, *original drugs* are medicinal products, put into circulation with registered proprietary names; reproduced *drugs (generics)* - drugs put into circulation after expiry of exclusive patent rights to the original drugs.

The emergence of a large number of generic drugs on the market has led to the need to assess their equivalence to the original drug.

Three types of equivalence are distinguished: *pharmaceutical, biological* and *therapeutic*.

Medicinal products are pharmaceutically equivalent if they contain the same quantity of the same active ingredient(s) in the same dosage forms that comply with the same or comparable standards.

Pharmaceutical equivalence does not necessarily imply bioequivalence, as differences in excipients and/or manufacturing process may lead to faster or slower dissolution and/or faster or slower absorption. As a result, they may differ significantly in therapeutic efficacy and the severity of adverse effects.

In addition, differences in the preparation technology of individual medicines may also lead to differences in shelf-life.

According to the definition proposed by WHO experts "two medicines are considered bioequivalent if they are pharmaceutically equivalent, have the same bioavailability and, when administered in the same dose, have similar efficacy and safety". When determining bioequivalence, they recommend the use of the original

medicine as the reference drug. If the originator drug cannot be used, they recommend using the drug as a standard, leading drug on the market in a given country if its quality safety and efficacy are confirmed. In the absence of a leader drug, the generic drug to be registered should comply with the requirements of the local national or regional standard as well as the International Pharmacopoeia and “The WHO Guide to Registration Requirements for Determining Interchangeability of Medicines Produced by Multiple Manufacturers".

Drugs are considered therapeutically equivalent if they contain the same active ingredient and show the same efficacy and toxicity when administered to the same subjects. Therapeutically equivalent medicinal products must have proven efficacy and safety, be pharmaceutically and biologically equivalent, have similar instructions for use and be produced in accordance with GMP (Good Manufacturing Practice) standards.

# Chapter 4. Relationship between pharmacodynamics and pharmacokinetics. Dependence of effect on plasma drug concentration

The effect of a drug can be quantified using various characteristics. A distinction is made between *potency* and *efficacy* of a drug.

*The potency* refers to the ratio of the amount of a drug substance to the severity of its effect. Differences in potency are usually not of significant clinical importance, as it is usually possible to select doses equivalent in potency to those of different drugs, i.e. to ensure equal therapeutic effect.

As already mentioned, drug efficacy refers to the extent to which a drug has a positive effect on the course of a disease, i.e. the ability of the drug to have the greatest possible effect. For example, if drug A is able to produce an effect that cannot be achieved by prescribing drug B, even in the maximum tolerated dose, then drug A has greater efficacy. Differences in therapeutic efficacy have important clinical implications.

The dependence of the severity of the effect on dose is plotted in the form of a dose-effect curve. The "X" axis represents the dose and the "Y" axis represents the severity of the response (effect). Since usually even a small increase in dose leads to a significant increase in effect, a semi-logarithmic scale is used. It can be clearly seen that the higher the dose, the stronger the effect. However, from a certain level, a further

increase in dose may be followed by a decrease in the increase in effect and then the increase in effect stops altogether. Unwanted effects are more likely to occur with medicines whose effects increase sharply with increasing doses. The ratio of safety to efficacy of a drug is described by an index determined in animal experiments, the *therapeutic index*. This index is calculated as the ratio of 50% of the lethal dose to the effective dose.

Usually the patient receives the medicine at certain intervals. Although the relationship between drug dose and plasma concentrations is linear (Fig. 4.1), the dose-response relationship can not be observed for all drugs. This is due to the pharmacokinetics of the respective agents (“saturation” the absorption process, the variability of the effect of first passage through the liver and the degree of binding to blood proteins, differences in affinity to the target, etc.). In this regard, a more objective characteristic of the efficacy of a drug is the dependence of its action on the drug concentration in blood plasma, which is displayed by the curve "concentration-effect" curve (Fig. 4.2). This curve is based on the results of examination of a number of individuals, usually healthy volunteers, and is an averaged characteristic of the drug rather than an individual characteristic of the subject. From this curve, a very important indicator of drug action, the minimum therapeutic concentration or minimum therapeutic level, can be found. This level is the concentration at which 50% of the effect is achieved (effect, equal to 50% of the maximum). For most drugs there is also a “concentration-effect curve" for undesired effects. Together both curves define the allowable minimum and maximum plasma concentrations of the drug. The interval from the minimum therapeutic level to the concentration at which the first signs of toxic effects appear is called the therapeutic range (therapeutic window or safety corridor). The ratio of the upper limit of the therapeutic range to the lower limit is called *therapeutic latitude* and serves as a quantitative characteristic of the safety of the drug. It should be reiterated that the concentration-effect curve reflects an averaged pattern in a group of patients and can only serve as a general guide when treating a particular patient.

A graphical representation of the dynamics of plasma drug concentration can be referred to as the concentration-time curve. If two horizontal lines corresponding to the minimum and maximum therapeutic concentration are plotted on this graph, a visual representation of the therapeutic range is obtained (Figure 4.3).

Adequate dosing of a drug has the aim of maintaining its concentration within this interval. The therapeutic range may be shifted upwards if the patient develops tolerance to the drug in question or if it competes with another drug. In these cases, higher plasma concentrations are required to obtain a therapeutic effect (although without exceeding the maximum tolerated single and daily doses). In cases of hypersensitivity or in synergy with other medicines, the therapeutic range is shifted

downwards and a lower plasma concentration is required to achieve a therapeutic effects, the doses are reduced and the frequency of administration is reduced.

A direct correlation between the pharmacological effect and the plasma concentration of the drug is not always observed. A disruption of this relationship can be observed if the drug irreversibly alters the activity of the target (receptor, enzyme, etc.) and the recovery of its function is not related to the dynamics of the plasma concentration, but determined by the time required for the resynthesis of the target. For example, a single dose of acetylsalicylic acid (aspirin), which irreversibly inhibits cyclooxygenase, inhibits platelet aggregation for a period significantly longer than the drug's detection time in blood. Since uncultured platelets are unable to synthesise proteins, including enzymes, platelet aggregation will be restored after a significant renewal of the latter's pool. If we consider that the life span of a platelet is 10-14 days, then less than 10% of platelets capable of aggregation. This phenomenon has to be taken into account when planning surgical interventions.

Quite often, the relationship between the plasma concentration of the drug and the effect is not detected due to the fact that the clinical effect is not due to the drug itself but to its active metabolite. In addition, such a relationship is also not detected in cases not the free fraction but the total drug level with a high percentage of binding to blood proteins.

The absence of a direct effect-concentration relationship in some drugs is due to the presence of several points of application through which differently directed actions are mediated. For example, the hypotensive drug clonidine (clopheline) has a reduced effect if the optimal plasma concentration is exceeded. This is because high plasma concentrations lead to a predominance of peripheral hypertensive effects (due to the stimulation of alpha-adrenoreceptors) over the central hypotensive effect. This may also explain the paradoxical phase of action (increase in BP) of this drug when administered intravenously.

Where a concentration-effect relationship exists, plasma concentrations of difficult-to-dose drugs may be determined repeatedly throughout the course of treatment to ensure safe use. This monitoring is called *therapeutic monitoring*. Therapeutic monitoring is justified when the effect of a drug is difficult to quantify, e.g. in the prevention of epilepsy, arrhythmias; when using drugs with low therapeutic latitude (aminoglycosides); for diagnosing and correcting drug overdose. There is no point in therapeutic monitoring if the effect of the drug can easily be detected and the dose can be adjusted on this basis, e.g. by measuring the BP during hypotensive therapy, glycaemic levels during treatment with blood glucose-lowering drugs, etc.

Most drugs are eliminated from the body according to first order kinetics, i.e. the elimination rate is in direct relation to the concentration. This means that a constant percentage of the drug is eliminated from the body per unit time, which will determine the duration of the elimination half-life. Thus, for example, if the elimination rate of a drug is 12% per hour, the elimination half-life will be approximately 5.5 hours.

After $T_{1/2}$ the plasma concentration will decrease to 50% (by definition) of the initial level, after 2 $T_{1/2}$ to 25%, after 3 $T_{1/2}$ to 12.5%, and after 4 $T_{1/2}$ to 6.25%.

If the initial plasma concentration of the drug was within the therapeutic range, a level of 6.25% is generally well below the minimum therapeutic concentration. Therefore, it is generally accepted that after 4 $T_{1/2}$ after the last dose, the drug has no longer any pharmacological effect.

Some drugs are eliminated from the body according to zero-order kinetics, i.e. the intensity of elimination of these drugs does not depend on their plasma concentration or, more simply, the same amount of drug is eliminated per unit time. For example, 50 mg of a drug is eliminated in 24 hours, regardless of whether the amount in the body is 100 mg or 30 g. In some cases, this phenomenon occurs when the plasma concentration exceeds a certain level and elimination mechanisms, e.g. the enzymes involved, are "saturated". Such drugs do not have a half-life. This means that if their administration exceeds elimination, their plasma concentration will never reach a maximum and will increase continuously. The dosing of such drugs must be done particularly carefully because of the danger of overdose. There are few such drugs, among them acetylsalicylic acid in high doses (grams per day). The excretion of ethyl alcohol follows the same pattern.

The pattern of the concentration-time curve depends on the dosing regimen, which consists of the starting dose, the number of times the drug is administered and when the drug therapy is discontinued. Full clinical effect of an administered drug dose is achieved once a stable equilibrium concentration has been reached. When administering in drug therapy, an important condition for obtaining the desired effect is the speed of reaching the equilibrium concentration within therapeutic range.

As stated in Chapter 3, with adequate multiplicity of administration the time to reach the equilibrium concentration is 5-7 $T_{1/2}$. If the drug has a long elimination half-life, it takes a long time to reach equilibrium concentration and develop a therapeutic effect. In this case, if a rapid therapeutic effect is required, treatment should be started with shock (saturation) doses.

Stable equilibrium concentration has two important featurethe average plasma concentration of the drug is determined by the daily dose and there is a linear relationship between the two; for example, when the dose doubles, the average plasma concentration also doubles; fluctuations in plasma drug concentration are determined by the frequency of drug administration - for the same daily dose, more frequent administration will result in lower fluctuations in concentration; with continuous infusion, there are no fluctuations; prolonged and slow-release forms also produce lower fluctuations in plasma drug concentration; when the drug dose is changed (increased or decreased), the new plasma concentration, a new steady state concentration is reached (increased or decreased) after about 4 half-lives.

If the drug is continued after reaching the equilibrium concentration, the total amount of the drug in the body remains constant. In cases where it is necessary to reach this level quickly, an appropriate amount of the drug can be administered once. To estimate this quantity, multiply the expected average plasma concentration of the drug by its volume of distribution (these are reference values). However, the distribution is influenced by age, sex, total amount of fatty tissue, etc. The use of shock doses increases the risk of developing undesirable effects, especially of medicines with a low therapeutic latitude. Individual differences in pharmacokinetics also play an important role in these cases.

Regarding gradual incremental dosing regimens, it should be remembered that a minimum of 4 $T_{1/2}$ is required to achieve a stable plasma concentration and that no further dose increases are allowed until it is certain that the drug has no adverse effects.

# Chapter 5. Effect of Various Factors on Drug Action.

## 5.1 Specific features of clinical pharmacology in pregnant, lactating women.

Drugs taken by the mother during pregnancy may have adverse effects on the foetus and the newborn. No medicine, including topical ones, can be considered completely safe. Statistics show that at least 5% of all congenital anomalies are due to medication. The penetration of drugs through the placenta depends on their physico-chemical properties, the state of the placenta and the placental blood flow. When drugs have to be used, it should be borne in mind that most of them penetrate the placental barrier and their inactivation and excretion rates in the embryo and foetus are not high enough, increasing the risk of adverse effects on the foetus.

There are three critical periods in fetal development that differ in their sensitivity to damaging exogenous and endogenous factors:

- *1st week of pregnancy - the preimplantation development stage*. At this time, the toxic effects of the drug factors are most often manifested by the death of the embryo.

- *The stage of organogenesis*, which lasts about 8 weeks. The risk of fetal damage is particularly high during the first 3-6 weeks after conception. The drug used during this time in the treatment of the pregnant woman may:

    - have no visible effect on the foetus;

    - cause a spontaneous miscarriage;

    - cause a severe sublethal abnormality of the organ that was developing most intensively when the mother was taking the medicine (true teratogenic effect);

    - cause a minor but irreversible metabolic or functional abnormality (hidden embryopathy) that may manifest later in life.

- 18-22 weeks of pregnancy, when the fetus is rapidly changing the bioelectrical activity of the brain, actively forming the hematopoietic, endocrine systems.

Medication administered to a pregnant woman just before labour, can affect the course of labour and cause various disorders in babies, especially premature babies, in the first hours and days of life. Among the actions of drugs in pregnant women, embryotoxic, embryo-toxic, teratogenic and fetotoxic are distinguished.

Depending on the possible risk of adverse effects, drugs are divided into high, significant and moderate risk groups (Table 5.1).

**Table 5.1. Division of medicines according to the risk of adverse effects on the foetus**

| High risk drugs | Medium risk drugs | Moderate risk drugs |
|---|---|---|
| Cytostatics | Antibiotics | Sulphonamides |

| | | |
|---|---|---|
| Antifungals<br>Antibiotics<br>Antineoplastic antibiotics<br>Immunosuppressants<br>Sex hormones(androgens, diethylstilbestrol) | Antiprotozoal drugs (Aminoquinoline derivatives)<br>Anticonvulsants (phenytoin, carbamazepine)<br>Proivoparkinsonian drugs<br>Lithium salts<br>Glucocorticosteroids (systemic actions)<br>NSAIDS<br>Hypoglycemic oral agents<br>Neuroleptics<br>Ethyl alcohol<br>Indirect-acting anticoagulants<br>Antithyroid drugs (Mercazolil, iodides)<br>Bupivacaine<br>Mepivacaine | Metronidazole<br>Tranquillizers<br>Sex hormones (estrogens)<br>Articaine<br>Lidocaine<br>Propranolol<br>Diuretics |

Many countries use a classification of drugs based on possible risks of adverse effects on the fetus on the foetus, approved by The Food and Drug Administration (FDA) in the United States.

**Table 5.2. Categories of medicines, based on effect on the foetus, approved by the FDA**

| Category<br>Drugs | Effects on the fetus |
|---|---|
| A | Adequate and rigorously controlled studies have not no risk of adverse effects on the fetus in the first trimester and no evidence of this risk in subsequent trimesters trimesters. |
| B | Animal studies of reproduction have demonstrated no risk of fetal adverse effects, and adequate and well-controlled studies no fetal risks have been identified and there are no adequate and rigorously controlled studies No studies have been conducted on pregnant women. |
| C | Animal studies of reproduction have shown an adverse effect on the foetus fetal, and adequate and rigorously controlled studies in pregnant women have not been done. No adequately and rigorously controlled studies in pregnant women have been conducted, but the potential benefits Use in pregnant women may justify its use despite the risks it may pose. its use |

| | |
|---|---|
| | despite the risks it may pose. |
| Д | There is evidence of risk of harm to the fetus. There is evidence for a risk of harm to the human fetus in studies or practice, However, the potential benefit of the product in pregnant women may justify its use despite the risks it may pose. Pregnant women may justify its use despite the risks involved. possible risks. |
| X | Animal or clinical trials have shown evidence of fetal abnormalities and/or evidence of risk of harm. fetal development and/or there is evidence of risk of harm to the human fetus. X The risks associated with the use of the product in research or clinical trials or in practice; the risks associated with the use of the product in pregnant women outweighs the potential benefits. |

Mechanisms, adverse effects on the fetus of medicines obtained from the mother during pregnancy:

- ~ Indirect effects on the embryo, causing lethal, toxic or teratogenic effects; changes in the functional activity of the placenta (vasoconstriction) with impaired gas exchange and nutrient exchange between the mother and the foetus;
- ~ Disruption of the dynamics of biochemical processes in the mother's body, an interference with the physiological condition of the foetus;
- ~ Hormonal, vitamin, carbohydrate and mineral imbalances in the pregnant woman's body hormonal, vitamin, carbohydrate and mineral balances in the pregnant woman's body, negatively affecting the foetus.

The following points should be considered when prescribing medicines during pregnancy:

- ~ Influence of the drug on the pregnancy;
- ~ The effect of pregnancy on the effect of the drug.

Most medicines are able to pass through the placenta. The amount taken into the foetus is proportional to its concentration in the mother's blood and depends on the condition of the placenta. Placental permeability increases by the end of 32-35 weeks. Lipophilic, low molecular weight drugs penetrate the placenta better, and distribute rapidly to fetal tissue. The teratogenic effect may be due not only to the direct effect of

the drug entering the embryo, but also to the metabolic and uterine blood supply disturbances that it has caused in the mother.

Some medications are metabolised during passage through the placenta and toxic breakdown products may be produced. Once in the umbilical vein, they enter the fetal liver, where they are also metabolised. Since the activity of oxidative enzymes in the fetus is reduced, the metabolism of drugs is slow.

In toxemia of pregnant women due to fluid retention in the extracellular space the distribution of medications changes. Glomerular filtration decreases, hepatic metabolism is impaired, and the elimination half-life is prolonged, leading to higher plasma concentrations and possible development of toxic effects (Table 5.3).

**Table 5.3. Changes in drug pharmacokinetics during pregnancy.**

| Pharmacokinetic parameter | Direction of change | Note |
|---|---|---|
| Absorption | Decrease in late gestation due to slower gastric evacuation gastric to intestinal evacuation intestine | |
| Protein binding | Affects the rate and amount of the drug delivered through the placenta (the closer the relationship with the mother's proteins, the smaller the amount goes to the fetus) | Not significant for highly lipophilic drugs |
| Volume of distribution | Increase in the apparent volume of distribution of drugs due to an increase in BCC and total body weight | Has no clinical significance, at the same time, clearance increases and the bound fraction of the drug decreases |
| Metabolism | Reduced conjugation and oxidation increased sulphation No change in drug clearance drugs | |

| | | |
|---|---|---|
| | with high hepatic extraction | |
| Excretion | Increases glomerular filtration and elimination of drugs that are excreted mainly by the kidneys.<br>In late pregnancy, a slowdown in renal blood flow and a decrease in the excretion of drugs are possible | In late pregnancy, the excretion of drugs is affected by the position of the body of the pregnant woman |

Factors predisposing to the risk of adverse effects in the mother, fetus, newborn when a pregnant or breastfeeding patient undergoes dental treatment:

- ~ I trimester of pregnancy;
- ~ Repeated pregnancy, especially in a woman who has had multiple births;
- ~ Age of the pregnant woman (over 25 years old);
- ~ A history of obstetric and gynaecological complications;
- ~ A history of somatic diseases, especially diseases of the elimination organs (liver, kidneys, intestines);
- ~ Pregnancy with toxicosis;
- ~ The use of drugs penetrating through the placenta and into the breast milk;
- ~ Significant dosage of the drug;
- ~ The patient's neuropsychiatric condition and negative attitudes towards pregnancy and childbirth.

**Drugs and breastfeeding.**

Many drugs penetrate into breast milk and are absorbed by the newborn during breastfeeding. In general, it is advisable to stop breastfeeding if the mother needs medication therapy. Lithium, cytostatics, radioisotopes and narcotic analgesics in the mother's milk are particularly dangerous for the baby.

During lactation the use of vitamin A, NSAIDs (except paracetamol), atropine, barbiturates, benzodiazepines, high doses of vitamin D, systemic GCS, co-trimoxazole, lithium, erythropoietins and many antibiotics should be avoided. To avoid mistakes, the doctor should consult the instructions for use of the medication and the reference literature before making recommendations for drug therapy to the breastfeeding mother.

Effects on the foetus and the newborn of drugs used in

**1. Antibacterials and medications used in dental practice**

*Antibacterial preparations:*

During pregnancy, sensitivity to antibiotics may increase and the period of elimination from the body may be prolonged, which is particularly important for pregnant women with toxemia or pre-pregnancy renal lesions. In breastfeeding the use of broad-spectrum antibiotics may lead to changes in intestinal microflora, candidiasis, diarrhoea, hypovitaminosis, allergy in the child.

*β-Lactam antibiotics:*

~ Penicillins (especially semi-synthetic derivatives) are able to pass through the placenta, but there is usually no toxic effect.

~ Their degree of penetration through the placental barrier is inversely related to the degree of protein binding.

~ of their binding to plasma proteins. These drugs have no teratogenic or embryotoxic properties and can be used during pregnancy if the patient is not allergic to them;

~ Cephalosporins. No evidence of damaging effects on the foetus has been found.

~ They can be used during pregnancy (H.A. Hirsch 1971; V.G. Kukes 1999). When using them, the possibility of hypoprothrombinemia and the risk of bleeding due to reduced metabolism of vitamin K in the liver should be considered. During breastfeeding their undesirable effects in the form of fetal sensitisation and positive Coombs reaction.

*Lincosamides.* Lincomycin is contraindicated in pregnancy, the use of clindamycin is limited and its benefits must be weighed against the possible risks.

*Tetracyclines.* This group of drugs is not used during pregnancy in the first trimester of pregnancy, as they have adverse effects on foetal muscle development and inhibit skeletal growth. In the second trimester they may cause cataract, have a

hepatotoxic effect. When administered parenterally in the third trimester in pregnant women they may cause acute yellow liver dystrophy and acute pancreatitis.

It is important for the dentist to know that tetracycline administration is associated with impaired osteogenesis in fetuses and tetracycline deposition in the hard tissues with subsequent enamel hypoplasia and development of 'yellow teeth'.

Tetracyclines form chelate complexes with calcium orthophosphate and are incorporated into bone and dental hard tissue during calcification.

*Chloramphenicol* (levomycetin) can have teratogenic effects. It causes suppression of tissue respiration and damage to the cardiovascular system, which can lead to heart failure ("neonatal grey syndrome"). Most dangerous is damage to the hematopoietic organs with the development of hypoplastic anaemia. During breastfeeding high concentrations of the drug in breast milk are achieved, which may lead to inhibition of medullary hematopoiesis, development of jaundice or disruption of the intestinal microflora in the infant.

*Macrolides.* There is no evidence of teratogenic effects of drugs such as erythromycin, oleandomycin, clarithromycin, azithromycin, roxithromycin, etc., but there are reports of hyperbilirubinemia and inhibition of embryogenesis, and therefore macroids should be avoided if prescribed macrolides in pregnancy should be avoided. There is evidence of breast-milk penetration of clarithromycin and erythromycin.

*Aminoglycosides*. Adverse effects of the aminoglycosides (streptomycin, amikacin, kanamycin, gentamicin) have been associated with renal damage in the mother, lesions of the VIII pairs of cranial nerves in the mother and in the foetus, and various skeletal disorders in the foetus, so they should only be used if there are vital signs during pregnancy. The likelihood of complications is highest with streptomycin. Gentamicin and kanamycin are used only for vitally important indications.

*Fluoroquinolones*. Nalidixic acid, pipemic acid, norfloxacin, ofloxacin readily cross the placenta and accumulate in amniotic fluid. They have been shown in animal studies to cause fetal chondropathies, and although their teratogenic effects on the human foetus have not been confirmed, it is recommended that fluoroquinolones should be avoided in pregnant women. During breastfeeding, prolonged use of fluoroquinolones may have toxic effects on the infant.

*Sulfonamides*. Long-acting sulfonamides (sulfadimethoxin, sulfalene), and combinations of sulfonamides and trimethoprim (co-trimoxazole) are not recommended because they can have teratogenic effects at the end of the gestational period, which will manifest in the foetus and/or newborn with nuclear jaundice, methemoglobinemia,

erythrocyte haemolysis, bilirubin encephalopathy. Co-trimoxazole may additionally interfere with maternal and fetal folic acid metabolism due to trimethoprim. During breastfeeding, sulphonamides may actively accumulate in milk and cause hyperbilirubinemia, haemolytic anaemia (especially in glucose-6-phosphate dehydrogenase deficiency), kidney and liver damage and allergy in the infant. These drugs are contraindicated when feeding children under 6 months of age.

*Nitroimidazole derivatives*. Metronidazole significantly increases the frequency of chromosomal aberrations in human lymphocytes with carcinogenic effects on the foetus. Embryotoxic effects may occur in the first trimester and therefore nitroimidazole derivatives are not used during this period. In the second and third trimesters of pregnancy, they are administered only for vital indications. Anorexia, vomiting and blood dyscrasia in the neonate may occur during breastfeeding.

*Nitrofurans*. The use of furadonine, furagin, furazolidone, and furacilin is undesirable, as their use can cause blood haemolysis and hyperbilirubinemia in the postpartum period. They have a fetotoxic effect. Similar complications can occur with breastfeeding.

*Antifungal drugs* (levorin, amphotericin, griseofulvin, nystatin, natamycin, clotrimazole, fluconazole, etc.). Teratogenic effect was found in experiments with levorin, amphotericin and griseofulvin. No teratogenic and fetotoxic effects have been observed with nystatin, natamycin, clotrimazole and miconazole, bifonazole. Data on the use of triazole preparations in humans contain no information on the risks of their use, but animal experiments have shown their toxicity at high doses. Levorin, griseofulvin, amphotericin B, fluconazole, itraconazole should be avoided during breastfeeding.

2. **Non-steroidal anti-inflammatory drugs:**

Their action in pregnancy involves a blockade of prostaglandin synthesis, which can lead to complications in the form of a premature closure of the botanical gland, premature closure of the ductus botulinus in the foetus and formation of pulmonary hypertension, bleeding in the foetus and the pregnant woman.

NSAIDs in pregnancy should only be used in short courses and for strict indications, if this cannot be avoided. Paracetamol can be considered the drug of choice as an analgesic.

Salicylates and indomethacin have been shown to be teratogenic in animal studies. Prescribing these drugs in early pregnancy is not recommended, as even infrequent use of acetylsalicylic acid may have the following effects on the foetus:

- ~ embryotoxic, up to and including embryo resorption;
- ~ teratogenic, manifested in the postnatal period by cardiovascular abnormalities (hypoplasia of the left ventricle, interventricular septal defects with the development of pulmonary hypertension), diaphragmatic hernia;
- ~ delayed growth of the fetus, leading to congenital hypotrophy.

In the literature, there is evidence of fetal effects similar to aspirin in other NSAIDs (indomethacin, ibuprofen, naproxen, diclofenac). In newborns, the use of acetylsalicylic acid poses a risk of Reye's syndrome, and regular use at high doses may cause an anti-aggregant effect.

There is no evidence of adverse effects of other non-narcotic analgesics and anti-inflammatory drugs in the infant during breastfeeding, but most manufacturers recommend avoiding their use.

**3. Antihistamines**

The need for their prescription in a pregnant woman may be due to toxic symptoms such as nausea and vomiting in the morning hours. As histamine plays an important role in ontogenesis and regulates the metabolic relationship between the mother and the fetus, antihistamines should be avoided if possible.

Their use (especially of first generation drugs) in late pregnancy can lead to withdrawal syndrome in the neonate. Antihistamines penetrate little into breast milk and are therefore safe for the newborn.

**Peculiarities of dental interventions in pregnant women**

The details of preparing and carrying out dental interventions in pregnant patients are described in detail in special guides, but it is important to be aware of. A few general points to be aware of:

~ It is advisable to choose the time period between the 13th and 32nd week of pregnancy for a routine oral hygiene treatment of a pregnant woman. During this period, fetal organogenesis is complete, the formation of the placenta is completed or has already been formed, the foeto-placental circulation is functioning, the haemorrhage is stabilised to a certain extent.

~ hemodynamics is stabilised to a certain extent, the immunological status indicators have improved;

~ emergency dental care for pregnant women should be provided at any time, taking into account the concomitant pathology of the patient;

~ in any period of pregnancy, dental interventions should be carried out in an absolutely painless manner. Pain control is ensured by the use of appropriate local anaesthetics, psychotherapeutic support and, if indicated, premedication.

## 5.2. Effect of age, comorbidities, smoking, alcohol on clinical pharmacology of medicines.

**Effect of age on clinical pharmacology of medicines.**

***1. Drug therapy in children.***

Newborns, infants and young children have increased absorption of drugs when administered topically, especially if the skin and mucous membranes are inflamed. Therefore, systemic toxic reactions are possible when using ointments and creams containing GCS, antifungals, boric acid. Fatal outcomes have been described with burn sprays containing aminoglycosides and polymyxins.

Systemic glucocorticosteroids cause stunted growth and development in children. Close monitoring is essential if these drugs are used by inhalation.

**Table 5.4. Age groups in pharmacology.**

| | |
|---|---|
| Premature infants | 24-40 weeks |
| Newborn | 0-2 months |
| Babies | 2-12 months |
| Children | 1-12 years |
| Adolescents | 12-20 years |
| Adults | 20-65 years |
| Older | Older than 60 years |

*Practical aspects of medication use in children.*

*Medication dosing.* Simply reducing the 'adult' dose of a medicine may not be enough. Doses to children are calculated on the basis of age, weight or body surface area. But it is safest to use the medicine in the paediatric dose which is stated in the medicine's instructions for use. Most of the drugs approved for use in children have a paediatric dosage prescribed by the manufacturer.

*Choice of dosage form*. Children often refuse injections and have difficulty taking tablets or capsules, so preference should be given to oral liquid and topical preparations. Glucose-free alternatives, fitted with calibrated medicine spoons or pipettes, are an advantage.

*Informing the parents*. Parents should be told exactly how to take the medicine and how important it is to follow the doctor's recommendations exactly, including that treatment should not be discontinued after a subjective improvement in the child's condition. Parents should be tactfully informed about possible undesirable effects of the medicine and measures to detect and prevent them.

***2. Drug therapy in the elderly and elderly patients.***

Although the elderly are defined as patients over 65 years of age, ageing occurs at different rates in different individuals, and therefore individual differences in this category of patients are great.

*The importance of a specific geriatric pharmacology is due to:*

~ The increasing proportion of elderly and old people in the populations of developed countries. Thus, the number of people aged 75-80 years old on the planet is increasing annually by 2.4%, and in Russia they make up about 30 million people. At the same time, in developed countries 12% of the population are elderly and old people, and they consume about 25-30% of medicines.

~ Adverse drug reactions in this age group, which they develop 2-3 times more often than in young and middle-aged patients.

~ Polypragmasy, which is particularly common in this age group. On average, they take 3-4 drugs in outpatient treatment, which increases the risk of unwanted drug interactions.

~ Changed drug reactions due to decreased functionality of organs and systems, increased incidence of co-morbidities, nutritional disorders, non-compliance with the drug regimen.

~ -Decreased memory in elderly people, mental disorders, limited financial resources, various unfavourable social factors.

In older patients, the pharmacokinetic parameters of the drugs used change significantly (Table 5.5). This is due not only to age-related changes, but also to chronic diseases, eating disorders, and possible drug abuse (laxatives, NSAIDs, etc.).

**Table 5.5. Features of the pharmacokinetics of drugs in older age groups.**

| Pharmacokinetic parameters | Nature of change | Action result |
|---|---|---|
| Absorption | Reduced acidity of gastric juice, enzyme, pancreatic secretion activity gland.<br><br>Reduced motor gastrointestinal function, absorption intestinal surface due to atrophy of villi, mesenteric blood flow.<br><br>Chronic diseases.<br><br>Unbalanced diet.<br><br>Intake of antacids, laxatives, antispasmodics | Change in velocity, completeness of absorption medications, calcium, iron, thiamine, ciancobalamin |
| Dissipation | Reduction in muscle mass, water | Decrease in volume |

| | | |
|---|---|---|
| | Increase in fat<br>Circulation disorders (decreased cardiac output, velocity medication in blood flow, microcirculation)<br><br>Hypoalbuminemia | Reducing the volume of distribution and increasing the content of water-soluble drugs in plasma.<br><br>Increased volume, distribution and risk cumulation of fat-soluble drugs.<br><br>Disruption of transport of pharmaceuticals into tissues.<br><br>Increase in free active fraction drugs in the plasma and, consequently-therapeutic and unwanted effects. |
| Metabolism | Atrophy of the liver parenchyma, ALS, unbalanced and insufficient nutrition lead to a decrease in the activity of microsomal enzymes, hepatic blood flow | Increased presystemic metabolism drugs with high hepatic clearance, prolongation of T ½ and concentrations of drugs in the blood |
| Excretion | Reduced renal blood flow, glomerular filtration, quantities of functioning neuronal, tubular secretion<br><br>Decreased respiratory function | Prolongation of T ½ and drug concentrations in plasma<br><br>Reduced excretion of volatile drugs, restricted use of inhaled anaesthetics |

Pharmacodynamic features in older age groups, compared to younger patients, are due to a reduced number of specific receptors, while at the same time their

sensitivity to drugs may be increased and/or perverted. Decreased physical activity, impaired electrolyte balance, vitamin and mineral deficiencies and predominance of excitation over inhibition in the nervous system may transform drug responses. In general, elderly people are considered to be more sensitive to a number of drugs that should be restricted for them or should be administered with special caution (Table 5.6).

**Table 5.6. Drugs for which special caution is warranted in elderly patients.**

| Drugs | Adverse effects in elderly and elderly patients elderly patients |
|---|---|
| Lidocaine | Increased risk of unconsciousness, paresthesias, respiratory problems, respiratory distress, hypotension, seizures |
| Hypotensive agents | Risk of orthostatic hypotension |
| Beta-blockers | Change in sensitivity (increase or decrease), adrenoreceptors confusion when using lipophilic drugs, peripheral circulatory disorders, hypothermia |
| Nitrates | Decrease in BP, worsening of cerebral circulation |
| Beta-2-stimulants of adrenoreceptors | Decrease in sensitivity, effectiveness |
| Narcotic analgesics | Increased sensitivity, risk of respiratory collapse |
| NSAIDS | Risk of bleeding, hyperkalemia, renal failure |
| Glucocorticosteroids | Risk of osteoporosis |
| Antihistamines drugs | Increased sedation, urinary retention, Increased intraocular pressure in patients with narrowing of the anterior chamber anterior chamber |
| Phenothiazines | Orthostatic hypotension |
| Benzodiazepines | Increased sensitivity to diazepam, nitrazepam, flurazepam |
| Diuretics | Dehydration, electrolyte metabolism disorders (hypokalemia, hyperglycaemia, hyperuricaemia, arrhythmias |
| Aminoglycosides | High risk of nephro- and ototoxicity |

*Basic rules for prescribing drugs for the elderly:*

~ Necessity and feasibility of dose reduction should be considered.

~ Use creatinine clearance for dosage adjustment for drugs that are excreted unchanged through the kidneys.

~ In the case of metabolisable drugs, start with low doses.

~ Reduce the number of doses to 1-2 times a day.

~ Control treatment frequently, especially with drugs with a low therapeutic index.

~ Compile a card describing the medication, the regimen and the dose.

~ Use a medication dosing device.

When prescribing oral rinses, ointments, creams, denture preparations, warn the patient and relatives against taking them orally.

***3. Effect of smoking and alcohol on clinical pharmacology of medicines.***

Nicotine, benzopyrene and their derivatives are able to modify the activity of microsomal liver enzymes and accelerate the metabolism of several medications (theophylline, caffeine, propranolol, diazepam, aminazine). Therefore, smoking should be considered as a factor, inhibiting the efficacy of drug therapy.

Alcohol in chronic use increases the activity of hepatic enzymes, which increases the metabolism of medication and may lead to a decrease in their plasma concentration and therapeutic efficacy. At the same time, alcoholic liver damage disturbs biotransformation of drugs, which leads to prolonged elimination half-life, increased plasma concentrations and enhancement of both therapeutic, and toxic effects. This has been proven for barbiturates, benzodiazepines, isoniazid, furosemide, propranolol, ampicillin.

At the same time, the single use of alcohol inhibits liver microsomal enzymes and, by reducing the metabolism of drugs, increases their effects. Therefore, when alcohol and CNS depressant drugs are taken at the same time (benzodiazepines, barbiturates, hypnotics, clonidine), their central effects are intensified and a coma may

develop. Alcohol increases the effects of oral antidiabetic drugs and indirect anticoagulants. Certain medications (metronidazole, furazolidone, chloramphenicol, griseofulvin) when combined with alcohol impair its metabolism, with possible development of "antabuse-like effects" - headache, palpitations, nausea, vomiting, hypotension.

***4. Peculiarities of clinical pharmacology of drugs in chronic liver diseases.***

Patients with chronic hepatitis and cirrhosis have reduced hepatic blood flow, develop porto-caval anastomoses, through which drugs enter systemic circulation, bypassing the liver. Microsomal oxidation is impaired due to hepatic cellular insufficiency. All these changes are accompanied by decreased metabolism, increased elimination half-life and increased plasma drug concentrations. Additional factors that increase the risk of toxic effects are hypoalbuminemia, cholestasis, hepatic encephalopathy. In patients with chronic liver disease, drug doses are reduced. Drugs should be used with great caution, controlling the development of undesirable drug effects.

***5. Peculiarities of clinical pharmacology of drugs in chronic kidney disease***

Impaired renal function with the development of chronic renal failure dramatically increases the risk of drug overdose and development of toxic reactions.

Renal clearance decreases in proportion to the impaired renal function. The risk of overdose is particularly high for drugs that are excreted mainly by the kidneys in unchanged form or as active metabolites. Additional factors that increase the risk of drug therapy in renal disease are hypoalbuminemia, anaemia and reduced renal metabolism of some drugs.

## 5.3 Effect of genetic factors

*Pharmacogenetics* is a branch of clinical pharmacology that studies the effects of heritability on drug pharmacokinetics and pharmacological response. This area of pharmacological research was formed by the late 50s of the twentieth century. The term "pharmacogenetics" was coined by Vogel in 1959.

Among the challenges facing clinical pharmacogenetics is the development of methods for the diagnosis, prevention and correction of the unusual response of the body to the action of drugs. Widespread use of pharmacokinetic studies and the

registration of hereditary variants of drug metabolism allow the results of pharmacogenetics research to be introduced into medical practice.

Genetic markers have been identified that allow an individual to be assigned to a particular biotransformation phenotype. Since the biotransformation of drugs in humans occurs under the influence of certain highly specific enzymes or groups of enzymes, represent specific proteins, mutations in the genes responsible for the production of these enzymes can lead to the formation of atypical enzymes and the development of enzymtopathies. In this case, a decrease in the content of the enzyme or a change in its activity is possible.

The most frequent genetic abnormalities concern the processes of oxidation, methylation and acetylation, leading to disturbed metabolism of some drugs, slows down their elimination from the body and contributes to the development of toxic effects.

The probability of gene mutations in a population can be assessed using statistical analysis methods. In recent years, methods for DNA diagnosis of enzyme disorders have been proposed and actively developed. Common inherited defects include deficiency in glucose-6-phosphate dehydrogenase (G-6-PDH), which plays an important role in carbohydrate metabolism, including in red blood cells, where it catalyses the oxidation of glucose-6-phosphate to 6-phosphogluconate. In this reaction reduced nicotinamide adenine dinucleotide phosphate (NADPH * H2) is formed, which is then used to reduce glutathione (with the help of glutathione reductase), and partially methemoglobin to haemoglobin. Reduced glutathione protects haemoglobin and thiol enzymes, which maintain normal permeability of erythrocyte membranes, against oxidative effects of various substances, including drugs. When taking a number of drugs (sulphonamides, nitrofurantoin, levomycetin) these people develop an acute haemolytic crisis due to a decrease in reduced glutathione and destabilisation of membranes. Hemolytic crises in these people are caused not only by medication, but also by horsemeat (lat. Vicia fava), so the disease is also called favism. The toxic substances in horse beans are hydrolysis products of B-glycosides (vicin and convicin), which have a strong oxidative effect 10-20 times greater than that of ascorbic acid. The disease usually begins suddenly, with chills and severe weakness, a drop in red blood cell count and then collapse.

Then collapse follows. Sometimes even infants whose mothers have eaten pork beans suffer from fauvism. The prevalence of the defect is highest in the Negro race (10-20%) and in Sephardic Jews of Asian origin (about 50%).

The number of people in whom the drugs in question cause hemolysis, varies in the population from 0 to 15% and in some locations as high as 30%.G-6-FDG deficiency and favism are common in Azerbaijan. In the 1960s, the cultivation of horse bean was banned in the country, which led to a significant reduction in the incidence of the disease. People with G-6-FDH deficiency should be warned about the dangers of appropriate medication and the need to exclude horse beans, gooseberries and red currants from their diet. Patients with G-6-FDH deficiency should be aware that their children may also have the same disease.

Another significant genetic abnormality is associated with the enzyme pseudocholinesterase, which is found in serum and various tissues and provides hydrolysis of choline esters and various aliphatic and aromatic acids. During administration of succinylcholine (dithiline) depolarising myorelaxant instead of expected short-term (2-3 minutes) relaxation of skeletal muscles, accompanied with respiratory arrest, a prolonged (2-3 hours) muscular paralysis associated with delayed drug degradation. The genetic defect of pseudocholinesterase formation is inherited recessively and its frequency in most populations does not exceed 2-4%, but in some populations the frequency of heterozygous carriage of the mutant allele is much higher. These are, for example, the Czech and Slovak populations (7%), the Jews of Iran and Iraq (10%). The frequency of homozygous carriage is as high as 1:400. In South India, the number of people with complete or almost complete absence of pseudocholinesterase activity is 2.5%. If prolonged apnoea occurs with succinylcholine, intravenous fresh donor blood with normal pseudocholinesterase activity should be administered. Succinylcholine is then rapidly is hydrolyzed and its effects cease. Intravenous administration of a solution of pseudocholinesterase isolated from donor blood has the same effect.

Some genetic abnormalities associated with altered drug action are shown in Table 5.7.

**Table 5.7. Genetic abnormalities leading to altered drug action.**

| Enzyme, its abnormality | Drugs and foodstuffs | Clinical manifestations |
|---|---|---|
| Glucose deficiency 6-phosphate dehydrogenase | sulphonamides, nitrofurantoin, levomycetin Horse bean | Haemolytic crises |
| Insufficiency methemoglobin reductase | nitroglycerine, sulphonamides, chloramphenicol, | Methemoglobinemia |

| | | |
|---|---|---|
| | para-aminosalicylic acid, antipyrine | |
| Atypical pseudocholinesterase | Succinylcholine | Prolonged paralysis transverse striated musculature with respiratory arrest respiration |
| Increased activity Synthase d-aminolevulene acids | barbiturates, sulphonamides, estrogens, amidopyrine, diclofenac, griseofulvin, some tranquillisers and anticonvulsants, alcohol | Porphyria (seizures intestinal colic, polyneuritis, seizures, muscle paralysis, psychiatric disorders and etc.) |
| Inadequacy acetyltransferase | Isoniazid, sulfadimesin, hydralazine, prazosin | Headache, dizziness, nausea, vomiting, chest pain, irritability,insomnia, tachycardia,polyneuritis etc. Undesirable effects due to delayed drug metabolism |
| Catalase deficiency (see Chapter 27) | Hydrogen peroxide | Recurrent inflammatory processes in the oral inflammatory processes with ulceration gum atrophy, loss of teeth, in more severe cases - alveolar gangrene with extension to the soft tissue and jawbone soft tissue and bone of the jaw. |

## Control questions.

1.In pregnancy, it is considered safest to use medicines in the following FDA classification categories:

a) Category A
b) Category B
c) Category C
d) Category D
e) Category X

2.The greatest risk of developing adverse drug effects on the foetus is:

a) in the first 8 weeks of pregnancy
b) at 18 to 22 weeks of pregnancy
c) at 26 to 28 weeks of pregnancy
d) correct A and B
e) all correct

3.It is safest to use as an anaesthetic for non-serious dental interventions in pregnant women:

a) bupivacaine
b) mepivacaine
c) droperidol
d) articaine
e) all of the above drugs can be used

4.Penetration of a drug through the placenta is influenced by:

a) the molecular weight of the drug
b) the lipophilicity of the drug
c) the gestational age
d) ability of the placenta to metabolise the medication
e) all of the above

5.Doses of medication are reduced in:

a) children
b) women

c) breastfeeding mothers
d) correct A and B
e) all of the above are correct

6. In the elderly, the risk of relative drug overdose is due to:

a) impaired absorption of drugs
b) decreased activity of hepatic microsomal enzymes
c) increased hepatic blood flow
d) decreased reabsorption in renal tubules
e) all of the above

7. In elderly patients, drug absorption is affected by all factors except:

a) decreased acidity of gastric juices
b) ingestion of laxatives
c) increased body fat
d) decreased enzymatic activity of pancreatic secretion
e) atrophy of the villi of the gastrointestinal mucosa

8. In chronic alcohol intoxication with liver damage, the elimination half-life is increased:

a) barbiturates
b) benzodiazepines
c) propranolol
d) correct A and B
e) correct A, B and C

9. A factor contributing to the increase in plasma concentration of the free drug fraction in CPH is:

a) impaired renal excretory function
b) hypoalbuminemia
c) decreased presystemic hepatic elimination
d) correct A and B
e) correct B and C

10. Pharmacogenetics studies:

a) congenital malformations caused by the action of drugs
b) genetically determined changes in the pharmacokinetics of drugs
c) changes in the sensitivity of micro-organisms to antibiotics due to gene mutations
d) drug bioequivalence
e) all of the above

# Chapter 6. Adverse drug reactions. Drug Dependence

## 6.1 Undesirable drug effects

Drug-related morbidity and mortality is a major problem in modern medicine: each year in developed countries 10-16% of patients admitted to hospitals, are hospitalized due to complications of drug therapy, and in several thousand patients they are the direct cause of death.

As defined by WHO experts, the term *adverse effect of the drug(AED)* refers to any harmful and undesirable reaction to the human body developed when using the drug in typical doses used for treatment, prevention or diagnosis of diseases. Individual characteristics of the patient play an important role in the development of this undesirable reaction and its occurrence is not due to an overdose of the drug. A reliable link between ND and drug intake can be assessed if the reaction has disappeared after drug withdrawal and has occurred again after re-taking the drug.

### Classification

None of the existing classifications of AED is perfect. From a practical point of view, it is useful to divide these reactions into several types, depending on the nature of the course, localization, degree of severity and frequency.

### Classification according to the nature of the course

***Type A reactions*** are frequent, predictable AEs resulting from a known pharmacological mechanism. They are dose-dependent (known as booster) reactions that can be observed in any patient. Depending on the cause, three reactions are distinguished:

a. pharmacokinetically induced
b. pharmacokinetically induced
c. pharmacodynamically induced

***Type B reactions*** are non-dose related, non-predictable AEs that may occur in individual susceptible patients. These drug effects are usually detected and reported several years after the start of widespread use of the drug in general practice. Depending on their causes, a distinction is made between:

a. immunological reactions
b. pseudo allergic reactions
c. genetically determined

***Type C reactions*** - effects that occur with long-term use of medicines: drug dependence, the phenomenon of withdrawal, resistance and the associated reduction in the effectiveness of therapy. Sometimes this group also includes a variant of the toxic effects (see p. of effects), which is caused by a drug cumulating in the tissue over a long period of time (possibly over  years), as well as various paramedical (see p30) reactions.

***Type D reactions*** are delayed AE: carcinogenic, mutagenic and teratogenic effects.

Toxic reactions associated with accidental or deliberate absolute overdose of a drug are of particular concern. Examples of such reactions are the development of coma in persons who have taken large doses of sleeping pills, acute hepatic failure when taking paracetamol in doses of several times the maximum permissible dose. Acute liver failure may be caused by the use of paracetamol at doses several times the maximum permissible dose. Study of the clinical picture, development of diagnostic methods and treatment measures for these conditions is a subject of medical toxicology.

**Type A reactions**

These AEs are largely due to the presence of concomitant chronic diseases, the initial state of internal organs, individual pharmacogenetic characteristics of the patient. They occur less frequently with drugs with a wide therapeutic index and are more likely when using drugs with a narrow therapeutic range (anticoagulants, aminoglycosides, local anesthetics, antiarrhythmic drugs, etc).

1. Pharmaceutically induced AEs depend on the quality of the drug. For example, the development of pyrogenic reaction and bacteraemia when using intravenous forms contaminated with bacteria or pyrogens. The use of expired preparations may also be accompanied by adverse reactions to breakdown products, in particular the development of Fanconi syndrome due to the action of tetracycline breakdown products. Changes in systemic availability of the active substance due to substitution of excipients are possible. For example, increased availability of phenytoin when replacing calcium sulphate calcium sulfate to lactose led in 1960 to an "epidemic" of complications from its use in Australia.

2. Pharmacokinetically driven AEs due to changes in drug concentrations. In this case, the drug is not only associated with an increase in its effect and development of toxic reactions, but also with a decrease of its therapeutic effect. May have as their basis:

a. Pharmacogenetic causes (see Chapter 6) - congenital, genetically determined retardation and reduction of drug metabolism.

b. Changes in drug absorption - influenced by drug composition, timing of drug intake and its relationship to food intake, motor and secretory function of the gastrointestinal tract, comorbidities, drug and food interactions, etc.

c. Distribution - affect regional blood flow, plasma protein content, tissue binding, drug interactions.

d. Metabolism of drugs in the liver, altered by impaired liver function or delayed excretion via the kidneys in renal failure. In such cases, a reduction in the maintenance dose is required.

e. Drug interactions, e.g. when coadministered with drugs that affect the cytochrome P450 enzyme system (see Chapter 8).

3. Pharmacodynamic interactions occur due to a reduction or increase in the number of receptors, changes in receptor sensitivity including those due to disease, genetic (racial) characteristics, electrolyte imbalances. Observed with the use of several drugs, with the same type of action.

**Type B reactions.**

Immunological - characterized by lack of relation to pharmacological action of the drug, dose-dependence, interval between first exposure to the drug and occurrence of subsequent undesirable reactions. Therefore, all so-called, allergy tests are potentially dangerous.

Risk factors for the development of immunological reactions:

1. Peculiarities of the structure of medications. Macromolecules with the highest "immunogenicity": proteins (plasma, albumin, gamma-globulins, vaccines), polypeptides (insulin);

2. The use of pharmaceutical additives: stabilisers, preservatives (sodium hyposulphite, parabens, etc.)

3. Genetic factors that predispose to allergies: atopy in the past(eczema, hay fever, asthma, allergic rhinitis); children born to mothers with atopy.

Hypersensitivity reactions are divided into four types (Table 7.1):

*Type I (anaphylaxis)* - urticaria, rhinitis, bronchial asthma, angioedema, anaphylactic shock.

These are caused by the formation of cytotropic antibodies, primarily of the immunoglobulin E class (reactants), which are fixed on mast cells, basophils, bind to allergens circulating in the blood. This leads to the release of biologically active substances (histamine, serotonin, acetylcholine, slow-reactive substance). They provoke spasm of smooth muscles, reduction of capillary permeability, etc. Eosinophils, heparin, phospholipase, platelet-activating factors, prostaglandins. Anaphylactic reactions can be either early or delayed, lasting between 3 hours and 12 to 24 hours. In patients with bronchial asthma, both early and late reactions may be induced simultaneously.

*Type II (cytotoxic hypersensitivity)* - thrombocytopenia, neutropenia, hemolytic anemia. Reactions of this type are often caused by rifampicin, analgin, phenylbutazone, penicillin, cephalosporins, quinine, quinidine, metronidazole. Circulating IgG, IgM antibodies interact with a hapten that is bound to a cell surface or antigen. This is accompanied by complement activation and cell lysis.

*Type III (damage by immune complexes, the Arthus phenomenon).* Examples of reactions of this type include serum sickness, acute interstitial nephritis, exogenous allergic alveolitis, dermatitis when taking penicillins, NSAIDs. Antigen-antibody complexes (IgG) circulate in the blood of patients, which fix and activate the C3 component of the complement. The complex is deposited in the tissues, activating the complement and damaging the capillary endothelium. The reaction is induced 2-4 hours after antigen exposure, peaks after 6-8 hours and may last several days. Damage occurs where pathological immune complexes are more likely to be retained - kidneys, lungs, skin.

*Type IV (delayed hypersensitivity or cell-mediated immune reactions).* These include contact dermatitis caused by topical anesthetic, anti-inflammatory, anti-allergic creams and ointments, antibacterial and antifungal drugs for local use. In this case, T-lymphocytes are sensitised by the antigen and an inflammatory reaction develops on repeated contact.

**Table 6.1. Types of allergic reactions (Gell et Coombs, 1975**).

| Type | Effectors | Manifestations |
|---|---|---|
| I Anaphylactic | IgE, mastocytes | Urticaria, Quincke's oedema(aspirin), systemic anaphylaxis (protein procaine) |
| II Cytotoxic | Neutrophils, macrophages, IgG, IgM, NK | Haemolytic anaemia (penicillin, methyldopa) |
| III Immunocomplex | AG + AT | Serum syndrome (penicillin, hydrochlorothiazide) |
| IV Cellular mediated | T-lymphocytes | Contact dermatitis (furacilin; neomycin) |

**Table 6.2. Drugs that give cross-allergic reactions. (A.V. Karaulov, 2002)**

| Drug | Drugs causing cross-reactions |
|---|---|
| Penicillin | Natural, semi- and synthetic penicillins, cephalosporins |
| Levomycetin | Synthomycin |
| Streptomycin | All aminoglycosides |
| Tetracycline | All tetracycline antibiotics, olethrin, oleandomycin |
| Sulfonamides | Novocaine, trimecaine, dicaine, co-trimoxazole, almagel A, solutane, PASC, hypothiazide, sulfocamfocaine, furosemide, triampur, butamine, bucarban |
| Aspirin, other salicylates | All NSAIDs |
| Eufylline | Suprastin, ethambutol |
| Pipolfen | Aminazin, florpromazine, alimazine, tizercine, propazine, thioproperazine |
| Iodine | Solutane, cardiotrast, Lugol solution, enteroseptol |
| Piperazine | Cinnarizine |

*Pseudoallergic reactions* are clinically mimicking allergic reactions, but without an immunological mechanism. They are caused by the release of biologically active substances (histamine, serotonin) from mast cells under the influence of drugs. Reactions of this type include anaphylactoid reactions when taking aspirin, vancomycin, anaesthetics, radiopaque agents, haemolysis with sulphonamides, and a skin rash with

ampicillin, which disappears without withdrawal. In the clinic it is often difficult to distinguish between pseudoallergic reactions and true allergic reactions.

*Pharmacogenetically induced reactions (iodosyncrasia)* are genetically determined pathological reactions to a drug. It is based on reactions caused by inherited defects in enzyme systems. These include haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, acute attacks of porphyria, etc. (see Chapter 5).

**Type C reactions**.

Among them are distinctioned:

~ Adaptive reactions of the organism, which manifests as the formation of physical, mental dependence (see page). When physical dependence develops, a tolerance to the drug and an increased need for it develops. At the same time withdrawal of the drug leads to development of withdrawal syndrome. Drug dependence is a variant of drug addiction, substance abuse and alcoholism;

~ Withdrawal syndrome, which can occur when a drug, such as a beta-adrenoblocker, is stopped suddenly and is associated with increased catecholamine concentrations, provoked ischaemia and myocardial damage. Another example is acute adrenal insufficiency syndrome following glucocorticosteroid withdrawal, the severity of which depends on the daily dose and duration of use. If a patient who has recently come off the medication is undergoing surgery, e.g. a tooth extraction, a short-term repeated treatment may be necessary, depending on the extent of the surgery. A short-term re-treatment may be necessary depending on the extent of the dental treatment (see also Chapter 2).

~ Decreased sensitivity, a slippage of effect when taking a drug for a prolonged period of time (see Chapter 2). An example of this is a reduction in the antianginal effect of nitrates when taken for a long period of time, which requires interruption of the drug for several days to restore sensitivity.

~ Paramedic AE refers to reactions due to psychogenic factors, e.g. after reading the package leaflet. In some cases, this can also include a decrease in therapeutic efficacy after replacing a drug that the patient is accustomed to with one made by a different company.

**Type D reactions.**

Reactions occur in a delayed period, therefore may not always be related to the action of any drugs.

*Carcinogenicity*. It is difficult to distinguish between an medication-induced tumour and a "naturally occurring" tumour. Data on the carcinogenicity of medications are based on the results of experimental studies and data from statistical studies, which are far from precise and unequivocal, and imply a long period of exposure to a carcinogen. It is now accepted that: women receiving oestrogen replacement therapy have an increased risk of developing endometrial cancer, there are increased incidences of bladder cancer in patients taking cyclophosphan, and an increased incidence of renal cell carcinoma in patients taking phenacetin.

*Reproductive disorders:*

~ Decreased fertility - Cytotoxic drugs lead to infertility in both men and women.

~ Teratogenic effects - Fetal development disorders are more likely to occur when medications are used in the first trimester of pregnancy. Some drugs are contraindicated later in pregnancy. This is discussed in more detail in Chapter 6.

Depending on the severity and severity of the clinical symptoms, AEs can be mild, moderate and severe. The severity of their clinical symptoms determines the tactics of care and the outcome:

~ Mild AEs do not require withdrawal of the drug, change in dose, additional treatment or, if hospitalized, extended periods of hospitalization;

~ Moderate AEs require a reduction in the dose of the drug, additional treatment may be required to correct the symptoms, and the length of hospital stay may be increased;

~ Severe AE requires mandatory withdrawal of the drug, mandatory drug therapy, with significantly longer periods of hospitalization;

The most severe outcomes of AE development are death, disability, carcinogenicity, teratogenicity, the need for hospitalization and long-term treatment.

Causes of fatal outcomes can be bleeding from ulcers of the gastrointestinal tract during long-term use of glucocorticosteroids, NSAIDs, anticoagulants; bleeding of other localization during therapy with anticoagulants and cytostatics. Fatal outcome may be due to aplastic anemia caused by phenylbutazone, cytostatics, chloramphenicol. Toxic liver damage from isoniazid, rifampicin, chlorpromazine, paracetamol can also lead to death. Renal failure caused by aminoglycoside antibiotics Generalised infections caused by glucocorticoids and cytostatics, anaphylaxis to proteinaceous drugs may also result in death. In outpatient practice, the most common reasons for hospital admission are AEs accompanying prescriptions of cardiac glycosides, NSAIDs, glucocorticosteroids, diuretics, anticoagulants and antihypertensive drugs. In the inpatient setting, AE associated with the use of potassium salts, opioid analgesics, antibiotics, insulin, cardiac glycosides, tranquilizers, infusion agents. When dividing adverse effects by localisation, local and systemic adverse effects are distinguished. It should be borne in mind that local application of drugs may cause systemic adverse effects associated with resorption of the drug from the site of application. For example, anaphylactic reactions when applying lidocaine solution or other local anaesthetic to the oral mucosa. In contrast, local adverse reactions may occur when a drug is used systemically due to both the general pharmacodynamic effects of the drug (xerostomia with atropine) and its local effects (see Chapter 8).

The clinical manifestations of AED are manifold, depending on the localization are presented in Table 6.3.

**Table 6.3. Clinical manifestations of AED.**

| Organ, System of organs | Symptoms and syndromes | Preparations |
|---|---|---|
| Skin and its derivatives | Exfoliative dermatitis, Steven’s syndrome, Johnson's syndrome, Lyell's syndrome | Penicillins, barbiturates, sulfonamides, salicylates, antidepressants, phenytoin, etc |
| | Urticaria, angioedema (Quincke's edema), maculopapular rash | Antibiotics, NSAIDs, ACE, antidiabetic medications, barbiturates |
| | Contact dermatitis | Topical application of antibiotics, NSAIDs, antiseptics |

| | | |
|---|---|---|
| | Photosensitization | Doxycycline, fluoroquinolones, phenothiazines, sulfonamides |
| | Discolouration of the skin due to hyperpigmentation or deposition of colouring pigments in the skin | Systemic and topical application; systemic use of glucocorticosteroids; bromides, amiodarone; ergotamine, preparations of mercury, silver (argyrosis), gold |
| | Hirsutism | Lithium preparations, vitamin B6, cyclosporine, calcium antagonists |
| | Hyperkeratosis | Vitamin A, arsenic preparations |
| | Alopecia | Cytostatics, heparin, beta-adrenoblockers |
| CNS and PNS | Headache | Nitrates, adrenaline, antagonists calcium |
| | Dizziness | Indomethacin |
| | Agitation, tremor and seizures | Diphenhydramine, aminophylline, ephedrine, lidocaine, phenothiazines, X-ray contrast agents |
| | Depression, psychosis | Clonidine, glucocorticosteroids |
| | Neuromuscular blockades | Aminoglycosides, beta-adrenoblockers, procaine, quinidine, D-penicillamine |
| | Peripheral neuropathies | Antiretroviral drugs |
| Cardiovascular system | Various disorders rhythm and conduction | Antiarrhythmics (proarrhythmogenic effect), beta-adrenoblockers, Cardiac glycosides (bradycardia, atrio-ventricular blockades), nifedipine, atropine, beta-adrenomimetics (tachycardia) |
| | QT interval prolongations | Cisapride, erythromycin |
| | Hypertension | Glucocorticosteroids, NSAIDs, Licorice |
| | Hypotension, including orthostatic and malignant | Diuretics, clonidine, prazosin |
| Respiratory system | Cough | ACE inhibitors, cromoglycate sodium |

| | | |
|---|---|---|
| | Bronchospasm | Beta-adrenoblockers, aspirin, acetylcysteine, gold salts |
| | Interstitial Pneumonitis | Cordarone, nitrofurans, methotrexate |
| | Pulmonary eosinophilic infiltrates | Nitrofurans, methotrexate, sulfonamides, carbamazepine |
| Gastrointestinal tract | NSAIDs and steroids gastroenteropathy, gastrointestinal bleeding | NSAIDs, glucocorticosteroids |
| | Dyspepsia (nausea, vomiting, diarrhoea) of varying severity | Oral antibiotics, (macrolides, tetracyclines, severity fluoroquinolones), cytostatics. |
| | Esophagitis | Cytostatics, theophylline. |
| | Pseudomembranous colitis | Antibiotics (more often beta-lactams, and lincosamides) |
| | Liver function impaired by intermittent hyperactivity Transaminases to hepatitis | Amphotericin B, ketoconazole, paracetamol, isoniazid, rifampicin, statins, antiviral drugs |
| | Cholestasis | Estrogens, anabolics |
| | Pancreatitis | Ascorbic acid, ethanol |
| Blood disorders and haemostasis | Thrombocytopenia, agranulocytosis, leukopenia, anaemia | Cytostatics, diltiazem, procainamide, chloramphenicol, sodium metamizole, amidopyrine |
| | Hypocoagulation and bleeding of various localizations | Anticoagulants, aspirin |
| Urinary system | Renal dysfunction due to renal blood flow disorder | NSAIDs, captopril |
| | Interstitial nephritis | Tetracyclines, allopurinol, NSAIDs |
| | Acute tubular necrosis | Aminoglycosides, X-ray contrast agents, diuretics |
| Musculoskeletal system | Osteoporosis with fractures of ribs, spine | Heparin, glucocorticoids |
| | Loss of muscle mass, myasthenia gravis and myalgia | Glucocorticoids |

| | | |
|---|---|---|
| | Rhabdomyolysis | Hypolipidemic drugs (statins, fibroic acid derivatives derivatives, nicotinic acid) |
| Endocrine system | Disorder Menstrual cycle | NSAIDs, glucocorticosteroids, oral contraceptives |
| | Gynecomastia and galactorrhoea | Metoclopramide, prazosin, anti-androgens |
| | Erectile dysfunction | Ketoconazole, beta-adrenoblockers (except bisoprolol), hydrochlorothiazide, bensidiazepines |
| | Virilisation | Androgens, anabolics |
| | Adrenal insufficiency | Dioxidine, withdrawal of glucocorticosteroids |
| | Hyperglycaemia | Diuretics, non-selective beta-adrenoblockers |
| Organs of vision | Glaucoma, posterior subcapsular cataract | Prolonged systemic use glucocorticosteroids |
| | Impaired accommodation | Atropine, aminotriptyline |
| Hearing organs | Decrease or loss of hearing | Aminoglycosides, diuretics (furosemide) |
| | Vestibular disorders | Vancomycin |
| | Tinnitus | Aspirin, indomethacin |

*Identification of adverse drug reactions.*

Before a new medicine is approved for clinical use and placed on the market, its safety is investigated in animal tests and in pre-registration clinical trials (Phase III) (see Chapter 10). However, the results from animal tests cannot be fully transferred to humans, and clinical studies are conducted on carefully selected groups of patients, are limited both in terms of numbers (around 5000 patients) and length of time. For example, 30,000 patients must be treated in order to identify at least one patient with a rare adverse reaction to the drug in use. When the drug enters the market, there is also insufficient information on the safety of its use in special patient groups (elderly, children, pregnant women, patients with kidney or liver diseases, etc.). This is why post-registration clinical trials to identify less frequent, but sometimes serious, adverse reactions are so important, as well as reports from practitioners to regional centres to regional centres about adverse drug reactions they have detected.

It is often difficult to diagnose AE because the reaction may be similar to, masked by, or delayed in time by the symptoms of the disease, be unusual and not perceived by the patient and physician as being related to the medication.

Still, there are a number of rules that help the physician in identifying undesirable effects of the drug:

- To be sure that the patient is receiving the prescribed medicine and in the dose that has been recommended;

- Develop the suspected effect of the drug after the start of the medication;

- Evaluate the course of the suspected adverse effect after withdrawal or dose reduction. In cases of non-serious adverse reactions, the drug may be reappointed to monitor for a return of the adverse effect. In case of type B reactions, re administration of the drug may lead to the development of a severe life-threatening reaction. All diagnostic confirmatory and provocative tests should be carried out in specialised medical centres;

- Evaluate other possible causes for the development of an undesirable effect;

- Consult with the manufacturer of the drug;

- Conduct laboratory diagnostic tests to detect internal organ damage (liver enzyme activity, blood creatinine clearance, clinical blood count, etc.).

In case of reasonable suspicion of an undesirable effect of a medicinal product in accordance with the requirements of the Federal Law "On Medicinal Products", health workers must inform the Federal State Institution "Scientific Centre for Expertise of Medicinal Products" of the Ministry of Health and Social Development of the Russian Federation by completing official notification forms.

## 6.2 Drug dependence

*Drug dependence* is a syndrome resulting from the use of certain medicinal products with the development of symptoms of discomfort upon cessation of their use and, in order to avoid the occurrence of this condition - the pathological need for further use of the medicinal product. In a broader sense, the term "addiction" is used with non-drug substances: alcohol, drugs, caffeine. In contrast to drug dependence, the use of

these substances is associated primarily with the development of euphoria - a pleasurable state that requires repeated use, which may require increasing doses to maintain.

*Addiction syndrome* is characterised by the development of what is known as *withdrawal* - a special condition manifested by emotional discomfort, dysphoria, anxiety, various autonomic disturbances and sleep disturbances etc. It is the presence of withdrawal that suggests the development of drug dependence.

Drugs such as narcotic analgesics, sleeping pills, tranquillisers and other psychotropic medications are particularly susceptible to causing drug dependence. A distinction is made between mental and physical drug dependence. In case of mental addiction, stopping the drug is mainly accompanied by emotional or psychological discomfort; in case of physical addiction, in addition to mental discomfort, significant autonomic disturbances occur.

In addition to addiction to pharmaceuticals, there is abuse of other drugs such as non-opioid analgesics, laxatives, antacids and enzyme preparations. Drug dependence and drug abuse have become a significant health, social and economic problem in developed countries. In the words of one researcher "... take a pill in the morning to wake up, in the evening to sleep, at lunchtime to aid digestion, at dinner to ward off obesity, a pill for the slightest ailment: for headaches, colds, general tonics, vitamins, etc., consuming dozens of drugs and hundreds of pills a week. Therefore, an important task of any doctor is not only to rationally prescribe medicines, but also to control their intake in order to avoid abuse and addiction.

## Control questions

1. Type B adverse reactions include all but:

a) anaphylactic shock to administration of novocaine
b) agranulocytosis to administration of analgin
c) haemolytic crisis when given sulphonamides
d) acute peptic ulcer when given piroxicam
e) fever when given ibuprofen

2. The development of adverse drug reactions is most likely in patients:

a) with chronic liver disease
b) suffering from bronchial asthma

c) elderly
d) with impaired renal function
e) in all of the above conditions

3. Type A adverse reactions are characterised by all but:

a) dose-dependent effects
b) kidney disease increases the risk of developing them
c) idiosyncrasies to the drug used
d) changes in receptor sensitivity to the drug
e) a connection with the mechanism of action of the medication

4. The criteria for the severity of an adverse drug reaction are all but:

a) life-threatening for the patient
b) embryotoxic effect
c) prolongation of hospital stay
d) persistent disability
e) developmental frequency

5. A patient has a history of anaphylactic shock to penicillin. The use of which antibacterial agent is contraindicated for him?

a) cefuroxime
b) tetracycline
c) ciprofloxacin
d) clarithromycin
e) co-trimoxazole

6. Type C adverse reactions include:

a) drug dependence
b) embryotoxicity
c) xerostomia
d) urticaria
e) drug-induced neutropenia

7. State the correct statement:

a) in patients with a history of allergic reactions, allergic skin testing is indicated before starting antibiotic therapy
b) injection of lidocaine is contraindicated in patients with novocaine allergy
c) drugs with a narrow therapeutic range are more likely to cause AEs of A type
d) the severity of the allergic reaction depends on the dose of the drug
e) the fetus is most sensitive to drugs in the third trimester of pregnancy

8. A risk factor for the development of AE is:

a) the presence of chronic sinusitis
b) drinking madications with coffee
c) alcohol abuse
d) age 20-45 years
e) short course of medication

9. Stevenson-Johnson syndrome is most commonly seen in patients, taking:

a) sulfonamides
b) digoxin
c) insulin
d) prednisolone
e) diphenhydramine

10. Photosensitization is possible when taking:

a) fluoroquinolones
b) aminoglycosides
c) furosemide
d) amoxicillin
e) metamizole

# Chapter 7. Adverse drug reactions in dentistry.

Although undesired effects of drugs are rare in dentistry, they can create serious problems in their interpretation, differential diagnosis and treatment. Firstly, a dentist may be the first to encounter an AE of medication, prescribed by a physician in another specialty, such as bleeding from the gums when taking indirect anticoagulants, or a local manifestation of a systemic reaction, such as ulcerative stomatitis in agranulocytosis caused by analgin. Second, the drugs used by the dentist can cause both systemic (hypertensive crisis when adrenaline is injected with local anaesthetics in a patient with hypertension) and local (burning of the perioral area from the use of dental elixir) effects.

## 7.1 Undesirable effects of medicinal products in the oral cavity during systemic use.

The most common systemic undesired effects are oral dryness (*xerostomia*) that may be caused by anticholinergic (atropine), some hypotensive drugs (clonidine, methyldopa), antihistamines (diphenhydramine), tranquillisers and other psychotropics (amitriptyline), sympathomimetics (fenoterol), diuretics. Xerostomia can also be associated with the accumulation of cytotoxic drugs in salivary gland tissue. It occurs in 21% of all oral lesions due to chemotherapy. It is reversible after withdrawal of the drugs or the use of agents that normalise the flow of saliva.

Xerostomia is accompanied by difficulty in chewing and swallowing, and may be complicated by an ascending salivary gland infection and trauma to the oral mucosa. Xerostomia leads to more rapid progression of dental caries and development of stomatitis.

In medical xerostomia, sugar-free chewing gum is recommended to stimulate salivary flow (sugar increases dental caries and supports infection). Artificial saliva preparations and gargles with solutions of citric acid, ascorbic acid and glycerine can reduce dry mouth. A 1% pilocarpine solution may also be used as a mouthwash. The increase in salivation could be made by betanechol (a cholinergic drug) that can be used sublingually as a tablet containing 5 or 10 mg of the drug. However, it should be taken into account that the drug itself may cause adverse reactions if used systematically (rhinorrhoea, lacrimation, intestinal colic).

Increased salivary gland secretion (*ptialism*) occurs under the influence of cholinergic drugs, mercury salts, iodides, bromides, ketamine, ACE inhibitors; as a

result of action on parasympathetic receptors (pilocarpine) or inhibition of cholinesterase (neostigmine).

Salivary gland pain (*sialgia*) can be caused by ornidine, octadine, guanethidine, methyldopa, betanidine, clonidine by central action or blockade of adrenergic activity leading to glandular hyperemia.

Phenylbutazone, iodides, including radiopaque agents, insulin, isoprenaline (isadrine), methyldopa, warfarin, phenothiazine, thiouracil, potassium chloride, sulfonamides can cause sialosis, which is an enlargement of the salivary glands with signs of inflammation and xerostomia.

*Taste disorders*: reduction (*hypoeusia*), loss (*agoeusia*), perversion (*dysgeusia*), e.g. sweet seems sour, can cause lithium salts, D-penicillamine, griseofulvin, metronidazole, lincomycin, acetazolamide, diltiazem, antidiabetic oral agents, levamisole. A musty taste in the mouth has been described with some antibiotics (penicillin). Altered taste is often combined with olfactory disturbances.

*Bad breath* accompanies the use of disulfiram, isosorbitol dinitrate (when taken under the tongue).

Local manifestation of *dysbiosis* due to use of glucocorticosteroids, antibiotics, immunosuppressants may cause secondary bacterial, fungal and viral infections in the mouth.

Discolouration of the oral mucosa and tongue is seen with methyldopa and oral contraceptives (light brown pigmentation). A bluish-green colouring of the oral mucosa is seen with phenothiazines.

*Blackening of the tongue* due to the growth of chromogenic bacteria in the papillae may occur with tetracycline, and due to salt deposits with copper, silver, zinc, gold, lead and bismuth.

Many madications can cause *discolouration of teeth*. A classic example is the yellowing of enamel with tetracycline antibiotics. Iron preparations can cause a similar effect.

The oral cavity is one of the earliest systems to react to the resulting clotting disorder with medications. It may be manifested by haemorrhagic rashes, bleeding gums, gum loosening. This may primarily indicate an overdose of anticoagulants,

aspirin and other antiaggregants. Increased bleeding of the gums may occur with secondary vitamin K deficiency caused by taking mineral oils, cholestyramine, warfarin, cefoperazone. A combination of symptoms of hypocoagulation, ulcerative necrotic stomatitis may be a manifestation of drug-induced agranulocytosis, pancytopenia.

*Gingival hypertrophy* develops as a consequence of taking cyclosporine, phenytoin, nifedipine and some other peripheral vasodilators.

Some medications cause *vitamin metabolism disorders*, manifested by some vitamin deficiency-specific oral lesions:

- *group B and folic acid* -hydralazine, D-penicillamine, levodopa, methotrexate, anticonvulsants (phenytoin, phenobarbital), triamterene, sulfasalazine, biguanides, para-aminosalicylic acid, cholestyramine;

- *fat-soluble vitamins*, primarily, *vitamin A* - vaseline oil,orlistat, cholestyramine;

- *vitamin C* - anticonvulsants, anorectics, tetracyclines, aspirin.

Drug-induced lesions of the oral mucosa may be similar to the manifestation of some diseases. Thus, *lichenoid stomatitis* (thickening of the oral mucosa, hyperpigmentation) observed against the background of the use of heavy metals (bismuth, gold salts, arsenic), allopurinol, chloroquine, tetracycline, quinidine, chlorpromazine, para-aminosalicylic acid, captopril, methyldopa, some NSAIDs, diuretics (furosemide, spironolactone), can simulate the manifestations *of red squamous lichen planus.*

*Dysquamous gingivitis*, similar to vesicular symptoms, occurs with D-penicillamine; a lupus-like syndrome has been reported with apressin, novocainamide, diphenine, isoniazid, methyldopa, amidopyrine, thiouracil.

One severe complication of cytostatic therapy is *mucositis* - this is an inflammation of the mucous membranes, with the formation of ulcers and erosions, in this background candida infection often sets in.

In dental practice, allergic reactions in the oral cavity are often seen as manifestation of a *systemic allergy*: multiple erythema during treatment with antibiotics

(tetracycline, penicillin, clindamycin), sulfonamides, salicylates, barbiturates, phenytoin, carbamazepine, phenylbutazone, isoniazid, meprobromate, amidopyrine; urticaria and orofacial Quincke's edema may occur as elements of an allergic systemic reaction to penicillin, lidocaine, aspirin.

Some of the specific effects of medications are given in Table 7.1.

**Table 7.1. Systemic adverse effects of some medictions in the oral cavity.**

| Drug | Oral manifestation of its LDs |
|---|---|
| Nifedipine, diphenine | Gingival hyperplasia |
| Cytostatics | Haemorrhagic rashes, xerostomia, mucositis, secondary infections, neuropathies |
| Estrogens | Mucosal pigmentation |
| Anticoagulants (warfarin, phenylline,heparin) | Haemorrhagic rashes, bleeding |
| Tricyclic drugs antidepressants, clonidine | Xerostomia |

## 7.2 Adverse effects of topical medication in dentistry

Medication can affect the soft and hard tissue of the maxillofacial region and can discolour teeth through direct exposure. For example, strong acidic or alkaline solutions, astringent or adsorbent products, toothpastes and mouth rinses can cause superficial mucosal desquamation and even ulceration. Substances such as phenol, silver nitrate, cresol, trichloroacetic acid, ethanol and acetylsalicylic acid will sting severely if used without care, the perioral area and the oral mucosa. Validol containing menthol may cause a burning sensation, pain and hyperaemia of the tongue - 'validol' tongue. Gentian violet, still sometimes used for the treatment of oral candidiasis, may cause superficial necrosis. Isoprenaline applied under the tongue sometimes causes ulceration of the mucosa of the cheeks and tongue, which usually disappears when the drug is withdrawn. Sometimes drugs with an acidic environment (hydrochloric acid, acidic solutions of isoprenaline salts) can cause tooth decay and decalcification.

Local allergic reactions as a result of contact of sensitised mucosa with the allergen: cheilitis, glossitis, stomatitis, are caused by menthol, thymol in toothpastes, gargle solutions, topical forms of analgesics, anaesthetics, iodides.

Contact allergy by the type of delayed reactions to the oral mucosa may be caused by denture and filling materials, methacrylate, dyes, cobalt-chrome alloys etc.

Fluorinated pastes sometimes give teeth a greyish-green tinge. Chlorhexidine gives teeth a greyish-brown colour. Tetracyclines can penetrate the crystal structure of dentin, causing discolouration of not only the surface, but also the deeper layers of the dental tissue. The teeth first take on a yellow colour, and then a gray color under the influence of sun exposure.

In all cases of superficial staining of teeth, harsh mechanical cleaning is applied. An important measure for the elimination of stained teeth is regular preventive care. The cosmetic problem in cases of deep staining of teeth has not been completely solved. Some authors recommend the use of a 35% hydrogen peroxide solution in a warm solution applied to the surface of the tooth. When inhaled glucocorticosteroids are used to treat obstructive lung disease in the form of aerosols, powders, some of the medication is deposited in the oral cavity and causes candidiasis of the mucosa. Patients with such diseases are therefore advised to rinse their mouth thoroughly after inhalation with baking soda solution and to use fungicidal agents.

Some local medications used in dentistry may cause undesirable effects due to their resorptive effects. For example, systemic effects of local anaesthetics (novocaine, xycaine) in the form of hypotension, nausea, seizures, arrhythmias, bradycardia. Concomitant administration of adrenaline with anaesthetics in some persons may cause increase in BP up to and including hypertensive crisis.

## Control questions

1. Oral candidiasis may occur with the use of:

a) pilocarpine
b) beclomethasone
c) phenylbutazone
d) oral contraceptives
e) lithium salts

2. Gingivitis develops with prolonged use:

a) phenytoin
b) diphenhydramine

c) warfarin
d) paracetamol
e) diltiazem

3. The colour of the oral mucosa changes under the influence of:

a) aspirin
b) methyldopa
c) clonidine
d) atropine
e) methotrexate

4. Sialgia is observed when taking:

a) tetracycline
b) metronidazole
c) clonidine
d) antidiabetic drugs
e) warfarin

5. Dental dislocation is possible with the use of:

a) diphenhydramine
b) chloroquine
c) methotrexate
d) vitamin C
e) chlorhexidine

6. Taste disturbances accompany taking:

a) aspirin
b) tetracycline
c) metronidazole
d) vitamin C
e) atenolol

# Chapter 8. Drug interactions. Drugs and food.

## 8.1. Drug interactions

*Drug interactions* are changes in the effect of one or more drugs (due to changes in pharmacokinetics or pharmacodynamics) when used concomitantly or sequentially. The changes may concern both therapeutic and adverse effects. A distinction is made between synergistic and antagonistic drug interactions depending on the end result.

*Synergism* is the unidirectional action of drugs resulting in a more pronounced effect than when each of these drugs is used alone.

A distinction is made between:

- *synergy*, which is when one of the drugs in the combination has a stronger effect than the other;

- *summation*, which is said when a combination of drugs gives an effect equal to the sum of the effects of each of the drugs included in the combination (AB = A + B);

- *potentiation*, where the total effect of the drug combination is said to exceed the sum of the effects of the drugs in the combination (AB > A + B);

- *additive effect*, observed in cases where the effect of a combination of drugs is greater than the effect of is greater than the effect of each of these drugs individually, but less than their combined effect (AB > A and AB > B, but AB < A + B).

*Antagonism* is a weakening or complete disappearance of part or all of the effects of one or more drugs used in combination.

*Clinically significant interactions* are observed for drugs with high concentration-dependence of effect, low therapeutic latitude, actively binding to blood proteins, altering (enhancing or slowing down) metabolism and excretion of other drugs. The likelihood of drug interactions increases when the number of concomitantly prescribed drugs increases.

Drug interactions are more common in elderly and senile patients, patients with hepatic and renal dysfunction, patients with diabetes mellitus, bronchial asthma,

epilepsy, patients in intensive care units. The likelihood of drug-drug interactions increases with the number of drugs prescribed. For example, patients receiving 6 or more drugs at the same time are 7 times more times more frequent than in case of a smaller number of drugs.

**Types of drug interactions**

Pharmaceutical, pharmacokinetic and pharmacodynamic drug interactions are distinguished, the latter being a physiological or pharmacological interaction.

*Pharmacological interaction* occurs either outside the human body (syringe, infusion solution, mixtures, etc) or in the GI tract prior to absorption and involves chemical or physical-chemical reactions between drugs in direct contact with each other. This may result in precipitation, new colour, different smell, etc. However, as a rule, the appearance of the mixture does not change, but the pharmacological properties of the drugs are lost, i.e. the interaction is antagonistic in nature. Examples include the interaction of acidic and alkaline solutions (a neutralisation reaction or change in optimum pH, resulting in a change in the chemical or physicochemical properties of one of the agents), oxidants (e.g. concentrated glucose) and reducing agents (e.g. ascorbic acid). In the same solution, cardiac glycosides are not compatible with aminophylline (euphylline), concentrated glucose, diphenhydramine (dimedrol), trimeperidine (promedol). Heparin rapidly loses activity in glucose solution and in the presence of hydrocortisone, and norepinephrine rapidly oxidises in isotonic sodium chloride solution.

Some substances are able through physical and chemical interaction to bind drugs, preventing the formation of their therapeutic concentrations in blood. First of all they include colloidal solutions: dextran (reopolyglucin, polyglucin), hydroxyethyl starch (infucol, reforman), povidone (haemodez); blood products, amino acid solutions, fat emulsions. All these preparations should not be used as media for preparing infusion solutions.

The ability of activated charcoal to adsorb various chemicals, which prevents drugs being absorbed into the gastrointestinal tract, is used to treat poisoning. Many drugs (tetracyclines, fluoroquinolones etc.) interact with ions of iron, magnesium, aluminum, bismuth, forming insoluble complexes, which leads to reduction of their effectiveness in combination leads to decrease of their effectiveness when combined with antacids containing aluminum and magnesium ions and bismuth preparations. In practice, the interval between the intake of an antacid and another drug should be 2-3 hours.

*Pharmacokinetic interaction* may occur at any phase of the pharmacokinetic cycle and may affect absorption, distribution, binding to proteins, metabolism and excretion. This is because one drug changes the concentration of the other in the blood, in the target organs, in the area where the mechanism of action is expressed and therefore changes the pharmacodynamic effect.

*Absorption phase*. The completeness and speed of absorption are influenced by:

- ~ gastric acidity, a decrease in which increases the degree of ionisation of drugs that are weak acids, which can impede their passage through biological membranes and reduce their bioavailability; decrease in gastric acidity under the influence of antacids, antisecretory drugs reduce the effectiveness of drugs such as NSAIDs, digoxin, sulphonamides;
- ~ GI motor function influences the speed of drug effect development and its severity, as absorption of most drugs in the proximal small intestine depends on the rate of gastric content evacuation; weakened gastrointestinal peristalsis under the influence of m-cholinoblockers (atropine sulphate, amitriptyline, etc.) and other drugs with anticholinergic activity (antihistamines, phenothiazines, opiates slows down absorption of many drugs and increases the time to reach maximum plasma level. ), other drugs with anticholinergic activity (antihistamines, phenothiazines), opiates slows down absorption of many drugs and increases time to reach maximum plasma concentration; at the same time prokinetics (metoclopramide - cerucal) accelerate evacuation of gastric contents, reaching maximum plasma concentration and development of the effect of various drugs; on the other hand, increased peristalsis also leads to reduced absorption of several drugsб e.g. digoxin absorption, when laxatives are administered;
- ~ the state of blood supply and microcirculation has an almost universal effect on absorption of all drugs, which is used to prolong local anaesthesia with vasoconstrictors, to suspend absorption of an intramuscular or subcutaneous drug that has caused a severe allergic reaction (anaphylactic shock or severe Quincke's oedema).

Some drugs selectively affect absorption of other drugs, although the mechanism of interaction is not always known. For example, PASC inhibits absorption of rifampicin and methotrexate, and acetylsalicylic acid inhibits absorption of diclofenac and indomethacin.

**Distribution phase.**

The distribution of the drug depends:

~ First of all, its *ability to bind to plasma proteins*. Drugs or their metabolites, which have high affinity to proteins, displaces other drugs from binding to them, which leads to higher concentrations of the latter in plasma, and may be accompanied by an increase in both therapeutic and adverse drug effects. This type of interaction is important for drugs that bind more than 85% to proteins and have a low volume of distribution. Examples are displacement from protein binding and increased plasma concentrations of free warfarin when combined with phenylbutazone. Some drugs can displace other drugs from their binding to tissue proteins.

An increase in digoxin in the blood has been described in the effect of quinidine, which replaces it in myocardial tissue.

Systemic and tissue blood flow affects the rate and extent:

~ distribution of drugs in the body. Drugs affecting cardiac output (vasopressors, cardiac glycosides), microcirculation (antiaggregants, anticoagulants), vascular tone and fluid volume (angiotensin converting enzyme inhibitors, alpha-adrenoblockers, diuretics) can affect the distribution, and therefore the degree of severity of pharmacological effects of other drugs.

~ it is important for clinical practice to improve drug delivery to lower bronchi due to bronchodilator effect of preceding or combined use of beta-adrenoceptors.

~ some drugs increase blood-brain barrier permeability to other drugs. Thus, eufillin, caffeine increase the level of penicillin in cerebrospinal fluid in meningococcal meningitis.

**Metabolism**.

Most of the drugs are biotransformed in the liver by various enzyme systems. Several drugs can increase or decrease the activity of microsomal liver enzymes that reduce or increase the metabolism of other drugs. For example, indomethacin and macrolides inhibit metabolism of many drugs, and phenobarbital and rifampicin

increase it. When combined with liver enzyme inducers, drug metabolism is increased and plasma concentrations are decreased, which is accompanied by a decrease in therapeutic activity. When combined with liver enzyme inhibitors, drug metabolism slows down and there is a risk of relative overdose and development of toxic effects. Therefore, when combined with liver enzyme inducers, the drug dose should be increased, and when combined with inhibitors, the drug dose should be decreased. Induction and inhibition of microsomal enzymes are reversible. After withdrawal of the inducer/inhibitor drug, the drug concentration returns to baseline.

The effects of drugs on enzyme systems may lead to the development of adverse drug interactions and this should be taken into account when choosing drug therapy. Alcohol, when taken regularly, induces enzyme systems and can inhibit the activity of many drugs.

Inhibition of microsomal enzymes is directly related to the dose of the inhibitor drug. When the plasma concentration of the inhibitor drug reaches an equilibrium level, the inhibitor drug the inducer drug reaches a new equilibrium concentration and the drug - object drug concentration is set at a new level. This means that a change in pharmacological effect develops quickly for drugs with a short half-life and takes longer for drugs with a long half-life. This type of interaction is most significant for drugs with a narrow therapeutic range. For example, administration of erythromycin to a patient who receives theophylline continuously may lead to a doubling of plasma concentration of theophylline and development of intoxication. Allopurinol has been described as fatal in patients receiving azathioprine or mercaptopurine. The same drug can act as both an inducer and an inhibitor.

For example, phenylbutazone enhances the metabolism of corticosteroids but, by inhibiting hepatic oxidases, slows the metabolism of chlorpropamide, phenytoin, butamide, warfarin.

**Table 8.1. Drugs that affect hepatic microsomal enzyme activity.**

| Inducers | Inhibitors |
|---|---|
| Aminazin | Allopurinol |
| Barbiturates | Amiodarone |
| Griseofulvin | Valproate |
| Diazepam | Verapamil |
| Carbamazepine | Diltiazem |
| Meprobamate | Disulfiram |
| Rifampicin | Isoniazid |

| | |
|---|---|
| Triptazine<br>Phenytoin (diphenin)<br>Chloral hydrate<br>Chlordiazepoxide<br>Ethanol (when used chronically) | Itraconazole<br>Ketoconazole<br>Metronidazole<br>Omeprazole<br>Oral contraceptives<br>Propoxyphene<br>Phenylbutazone<br>Chloramphenicol<br>Cimetidine<br>Ciprofloxacin<br>Enoxacin<br>Erythromycin<br>Ethanol (acute intoxication) |

The ability of one drug to inhibit the metabolism of other substances can be used for therapeutic purposes. For example, disulfiram blocks the metabolism of ethanol at the stage of acetaldehyde, which causes unpleasant feelings in humans (hot flashes, dizziness, shortness of breath, tachycardia, vomiting, intestinal cramps). This property is used in the treatment of alcoholism.

For drugs with a pronounced primary elimination effect through the liver (propranolol, verapamil), metabolism depends primarily on the magnitude of the hepatic blood flow and, to a lesser extent, on the activity of microsomal enzymes.

Therefore, drugs that reduce regional hepatic blood flow reduce the biotransformation of these drugs and increase their plasma concentrations.

**Excretion.**

The main drug interactions during the excretion phase take place in the kidneys. The drugs compete with each other for active tubular mechanisms. So quinidine, amiodarone, diltiazem, verapamil inhibit tubular secretion of digoxin, which is accompanied by increase of its plasma concentration and development of toxic effects. Combined use of furosemide and indomethacin leads to inhibition of tubular secretion of the former and reduces the excretion of the latter drug. The diuretic effect of furosemide is reduced, and the toxicity of indomethacin is increased. Furosemide reduces the clearance of gentamicin, levomycetin, penicillins and increases the toxic effects of these antibiotics. Probenicid reduces the excretion of penicillins and increases their plasma concentration.

Alkalinisation of the urine is caused by sodium bicarbonate (when the blood is alkaline), large amounts of isotonic sodium chloride solution and acetazolamide (in both cases if blood is acidified), thiazide diuretics - hydrochlorothiazide (if hypochloremic alkalosis may develop).

Ammonium chloride, salicylates, ascorbic acid cause acidotic shifts in urine. Most drugs are solutions of weak acids or bases. The degree of ionisation of the drug is affected by the acidity of the solution. Changes in urine pH can make a significant difference in the excretion of a drug. When urine is 'acidified', such as with sodium bicarbonate, the total clearance of 'acidic' drugs (NSAIDs, barbiturates, sulfonamides, salicylates). Excretion of codeine, morphine, novocaine is increased when urine pH is decreased, e.g. by ascorbic acid.

Drugs that alter renal blood flow may alter the glomerular filtration rate and excretion of other drugs. For example, digoxin, by reducing the clinical manifestations of chronic heart failure, increases renal blood flow, increases the excretion of furosemide and its natriuretic effect.

Interactions at excretion level are of particular clinical importance in initial renal dysfunction.

**Pharmacodynamic interaction**

*Pharmacodynamic interaction* - is a change in the site of action of a drug that is influenced by another drug. These interactions may be direct or indirect.

*Direct pharmacodynamic interactions.*

These interactions occur between drugs acting at the same site:

~ *competition for receptors* between drugs of unidirectional and opposite action. Examples of this type of antagonistic interaction are elimination of the effects of morphine under the influence of naloxone, or the lack of effect of beta-adrenoceptor stimulants in a patient taking a beta-adreno-blocker because the latter are more tightly bound to the receptor.

~ *decreased receptor sensitivity (desensitisation)* to a specific mediator by agonists or mediated by other drugs. For example, tricyclic antidepressants reduce the sensitivity of beta- adrenoreceptors to beta-adrenoceptors.

~ *an increase in the sensitivity and number of receptors* to one drug under the influence of another. A classic example is an increase in the number of beta-adrenoreceptors and their sensitivity to sympathomimetics by GCS. Fluorothane increases myocardial sensitivity to adrenaline.

~ *Changes in the kinetics (transport, transformation, binding) of a drug at the site of action under* the influence of another drug. Examples include. Increased effect of local anaesthetics when combined with adrenaline.

## 8.2 Drug and food interactions.

Food composition and timing have a significant effect on the bioavailability of an oral medication.

Food composition has an effect on the peristalsis and secretory function of the gastrointestinal tract, which the magnitude and rate of drug absorption. Fats reduce gastric secretion and inhibit gastric peristalsis, which leads to delayed food mass transportation, impaired digestion in small intestine and decreased therapeutic effectiveness of several drugs (antihelminthics, furodonin, sulfonamides). On the other hand fatty food increases absorption of fat-soluble drugs such as anticoagulants, metronidazole, diazepam, vitamins A, D, E and K.

The rate of gastric emptying increases with a low-fat, low-protein diet.

The passage of food through the stomach depends on the temperature of the food. As the temperature of food masses increases, the rate at which they are evacuated from the stomach increases.

It takes quite a long time for the drug taken with food to reach the main place of absorption - the small intestine. Consequently, when a quick effect is needed, the drug is taken on an empty stomach: 1 hour before a meal or 2 hours afterwards. However, in order to achieve a prolonged action of rapidly absorbed drugs with a short half-life, they should be taken after a meal.

As mentioned above, the acidity of the gastric juice affects the absorption of the medicines.

Macrolide antibiotics are partially destroyed by hydrochloric acid, especially erythromycin base and stearate, except for the enteric coated forms, which can be taken independently of meals.

Other antibacterials from the macrolide group are less susceptible to the damaging effects of hydrochloric acid. In an acidic environment, lincomycin hydrochloride is inactivated, and acetylsalicylic acid breaks down into ammonia and formaldehyde.

Chloramphenicol remains active and is absorbed over a wide pH range of 2 to 9, so that the food can be absorbed with its pH value.

Drinking medication with berry juices, tonic drinks and milk also changes the pH of the stomach and intestines. Acidic juices neutralise the effect of a number of antibiotics (erythromycin, ampicillin), increase the effect of salicylates, slow down the absorption of ibuprofen, furosemide. Do not wash down acid-coated drugs with milk as the protective coating dissolves and the drug will be destroyed before it reaches the place of absorption. Drinks contain various tannins, astringents, which interact with the drugs and may cause both potentiation and formation of insoluble, not absorbed complexes. The medicine should be taken with water, preferably boiled water, in an amount of 100ml.

In many cases, when prescribing drugs, an appropriate diet should be prescribed, so that food components do not alter the bioavailability of the drugs and do not cause undesirable effects.

For example, beans, nuts and other foods containing pyridoxine, which reduces the blood concentration of levodopa, are not prescribed in Parkinson's disease treatment. Diet containing folic or benzoic acid reduces the effect of sulphonamides.

Regular diuretics require a diet rich in potassium salts. Grapefruit juice increases the plasma concentration of a number of calcium channel blockers (dihydropyridine derivatives - nifedipine, nicardipine, felodipine, isradipine and verapamil).

A diet high in protein leads to an increase in plasma protein levels. The use of drugs with high plasma protein binding decreases free drug concentrations and is associated with decreased therapeutic efficacy. Such a relationship is shown for tetracycline, quinidine, theophylline, caffeine. Food affects the metabolism of drugs. Malnutrition, protein deficiency, especially in children, is accompanied by decreased activity of tissue oxidases, slower metabolism, excretion rate and prolongation of the period of action of some drugs (tetracycline, levomycetine, rifampicin, phenobarbital, morphine hydrochloride).

A diet high in tyramine and phenylethylamine (cheeses, feta cheese, cream, coffee, yeast, Riesling and Sherry wines), serotonin (pineapples, peanuts, bananas), dioxyphenylethylamine (beans, beans, bananas) when taking monoamine oxidase inhibitor antidepressants may lead to hypertensive crises. The patient should therefore be warned about dietary restrictions during treatment with these drugs.

Food rich in vitamin C stimulates oxidase function, speeding up drug metabolism, folic acid - speeds up diphenylhydantoin metabolism, vitamin B6 - reduces the effects of levodopa. Reducing plant foods in the diet may increase the effectiveness of anticoagulants.

In turn, the ingestion of the drugs can lead to impaired absorption of nutrients. This may be caused by damage to the epithelium of the small intestine mucosa, impaired microcirculation, motor and secretory function of the gastrointestinal tract, the normal composition of intestinal microflora as a result of the damaging effects of drugs.

Laxatives reduce absorption of all nutrients by increasing motor and secretory function of the intestine, incomplete digestion of food and speeding up defecation, disrupt intake and salt metabolism. Cholinomimetics also limit the absorption of nutrients from food, whereas atropine, prolongs the contact time of carbohydrates with the gastrointestinal mucosa, due to slowing the tone and motor function of the stomach and intestine, which increases the absorption of monosugars.

Prolonged use of diuretics leads to alkalosis, hypokalemia, protein deficiency, disorders of water-electrolyte balance.

Antibiotics damage gastrointestinal mucosa, cause dysbiosis, which is accompanied by abnormal gastrointestinal function, digestion process, development of diarrhea. Levomycetin inhibits the synthesis of intestinal mucosal cells of proteins necessary for the transport of nutrients.

Anticonvulsants, anticancer drugs, barbiturates, some neuroleptics disturb absorption of folic acid, vitamin B12 and vitamin D metabolism. The transport of amino acids is impaired under the influence of aminazine.

Thus, food significantly affects the effectiveness and safety of pharmacotherapy, and drugs, in turn, can change the absorption and absorption of nutrients.

## Control questions

1. Drug interactions can result in:

a) decrease in therapeutic efficacy
b) development of toxic undesired effects
c) increase in therapeutic efficacy
d) inactivation of one of the interacting drugs
e) all of the above

2. When tetracycline and an antacid are used in combination to prevent an undesirable drug interaction, the following should be avoided:

a) no antacid should be used
b) antacid should be taken before meals and tetracycline should be taken afterwards
c) the interval between doses of antacid and tetracycline should be 2 hours
d) take tetracycline before meals and antacid after meals
e) take tetracycline with meals

3: Drug interactions are most common with drugs that:

a) have high binding capacity with plasma proteins
b) often cause allergic reactions
c) have haematotoxic effects
d) are widely distributed in the body
e) all of the above are correct

4. In pharmacokinetic interaction of drugs:

a) interact chemically with each other
b) one drug alters the sensitivity of specific receptors to another drug
c) two drugs compete for a specific receptor
d) one drug alters the metabolism of another drug
e) the effect of one drug alters the potency of the other drug

5. A 46-year-old man suffers from chronic obstructive bronchitis 200 mg of theophylline daily. His dentist prescribed 2.0 g erythromycin daily for acute periostitis. After 3 days the patient experienced palpitations, heart palpitations, headache, tremor, agitation, insomnia. What is the development of these symptoms related to?

a) allergic reaction to erythromycin
b) slowed metabolism, increased theophylline concentration in blood and development of its toxic effects as a result of inhibition of liver microsomal enzymes by erythromycin
c) decreased renal clearance, increased blood concentrations and development of erythromycin toxic effects as a result of theophylline's action on renal blood flow
d) accelerated metabolism and excretion of theophylline under the influence of erythromycin and development of withdrawal syndrome
e) increased absorption, increased blood concentrations and development of toxic effects of theophylline due to the prokinetic action of erythromycin

6. What is the mechanism of drug interaction between local anaesthetic and adrenaline when used in combination in local anaesthesia?

a) physico-chemical interaction
b) increased sensitivity of specific receptors to local anaesthetic under the influence of adrenaline
c) decreased absorption and increased concentration of the local anaesthetic at the injection site under the influence of adrenaline
d) increase in absorption and systemic availability of local anaesthetic by adrenaline
e) decreased renal blood flow and decreased elimination of the local anaesthetic under the influence of adrenaline

7. A 61-year-old man receives 6 mg warfarin daily after aortocoronary bypass surgery. At the next follow-up examination the international normalised ratio (prothrombin ratio) is 8, while the target values for prothrombin is 2 to 3. He is also receiving enalapril 10mg daily and atenolol 100mg daily and in a week before the examination a dentist prescribed 2% cream containing miconazole for oral candidiasis. What is the cause of this reduction in blood prothrombin levels?

a) miconazole inhibits hepatic microsomal enzymes, which disrupts warfarin metabolism and increases its anticoagulant effect
b) miconazole inhibits hepatic microsomal enzymes, which impairs the metabolism of atenolol and increases its anticoagulant effect
c) enalapril inhibits hepatic microsomal enzymes, which disrupts warfarin metabolism and increases its anticoagulant effect

d) miconazole increases absorption of warfarin, which increases its anticoagulant effect
e) direct inhibitory effect of miconazole on prothrombin synthesis

8. When taking medication, it should be washed down with:

a) with milk
b) with fruit juices
c) boiled water AND mineral water
d) all of the above

9. Absorption of nutrients from food is reduced by:

a) atropine
b) laxatives
c) vitamin C
d) analgin
e) nifedipine

10. A diet high in fats:

a) decreases gastric secretion
b) accelerates gastric peristalsis
c) reduces the bioavailability of metronidazole
d) reduces the absorption of vitamin E
e) increases sulphonamide absorption

# Chapter 9. Preclinical and clinical evaluation of medicines.

The development and introduction into clinical practice of new drugs is a complex multi-step process of obtaining and analysing a vast amount of scientific data.

The development of new drugs includes the identification of the active molecule, preclinical trials (pharmacodynamics, pharmacokinetics, potential toxicity and safety of the new compound in the experiment) and clinical studies, the main purpose of which is to substantiate the therapeutic efficacy of the new drug and its safety in humans.

The period from discovery or synthesis of the potentially active molecule to production of the drug usually takes 8 to 12 or even 20 years, and development can cost up to 800 million US dollars and more. At the same time, out of 5,000-10000 chemical compounds with presumed therapeutic activity, on average, only 20

are further subjected to preclinical studies, 10 are included in phase I clinical trials, 5 in phase II and 2 in phase III clinical trials. Ultimately, only one of these is registered and approved for clinical use (Figure 9.1).

Figure 9.1. Selection of active chemical compounds in the drug development process.

## 9.1Doclinical trials.

In accordance with the provisions of the Declaration of Helsinki of the World Medical Association, which has laid down the basic principles of biomedical ethics, "Medical research involving human subjects must conform to generally accepted scientific principles and be based on a thorough knowledge of scientific literature, other sources of information, laboratory research and, if necessary, properly performed animal studies". The purpose of pre-clinical studies of medicines is to provide scientific methods for evaluation and evidence of their efficacy and safety.

The process of pre-clinical studies of a new medicine usually takes 2 to 4 years and includes *in vitro, in vivo* studies and the development of a dosage form(DF) of the medicine for further clinical trials in humans.

*In vitro laboratory studies* include synthesis, identification purification of a new active substance, study of its physico-chemical properties and biological activity.

Preclinical studies of medicinal products on animals (*in vivo*) are conducted in accordance with the international rules and ethical norms on the use of animals in scientific research (Animals Scientific Procedures Act, 1986).

Obligatory in preclinical animal studies are to determine acute, subacute and chronic toxicity, to study pharmacodynamics and pharmacokinetics, to identify possible mutagenicity, carcinogenicity and teratogenicity of the new drug. Studies are conducted on at least two animal species (mammals) using two routes of single or repeated administration. In addition, the efficacy of the new drug is being studied in experimental models of disease in animals.

In parallel with the *in vitro* and animal studies, pharmaceutical studies are carried out in order to obtain the optimal DF. The physico-chemical properties of the substance, its compatibility with other components of DF are taken into account.

However, the data obtained in the experiment can only be used as a preliminary guideline and cannot be directly transferred to humans. Therefore, after completion of preclinical studies on safety and efficacy, pharmacodynamics and pharmacokinetics of the new drug, after the creation of the appropriate dosage form it becomes necessary to conduct further clinical trials of the drug on humans.

## 9.2 Clinical trials. Requirements for clinical trials

*A clinical trial* is "...any study involving human subjects that has the goal of discovering or validating clinical pharmacological and/or pharmacodynamic properties of one or more investigational health product(s), and/or adverse reactions to one or more health product(s), and/or studies of absorption, distribution metabolism and excretion of one or more medical products in order to demonstrate their safety and/or efficacy. (EU Directive)

# Chapter 11. Principles of evidence-based pharmacotherapy.

The term 'evidence-based pharmacotherapy' is a subset of the more general term 'evidence-based medicine' or 'evidence-based medicine'. Evidence-based medicine is currently defined as "*the conscientious, accurate and meaningful use of the best clinical trial results to select a particular patient's treatment*". For the patient, evidence-based medicine is the guarantee of the most effective and cost-effective treatment, based on the best available evidence.

Evidence-based medicine should form the basis of the modern physician's worldview, including, above all, a new approach to the collection, analysis, synthesis and interpretation of scientific information. The main task of evidence-based medicine is to provide the physician with a methodology for finding objective answers to clinical questions, making maximum use of the knowledge accumulated in this field by the entire world scientific community.

A typical algorithm for making a decision (answering a clinical question) while observing the principles of evidence-based medicine looks as follows:

1.Formulation of the question.

2.Selection of sources of information.

3.Searching for clinical trial results.

4.Analysis of studies:

a) Screening out studies that do not answer the clinical question of interest;
b) Screening out studies with low level of evidence.

5.Formulation of clinical response (recommendation, decision).

**Formulation of the question**.

The clinical question, as is readily apparent, arises in the course of a physician's practice.

It most often concerns the choice of the most effective and safest therapy (not only pharmacological) or diagnostic method in a particular situation. If a doctor is prepared to admit that he is not sure about something or does not know something, questions will constantly arise in his daily clinical practice. The most important questions are often asked directly or indirectly by patients - "How will my condition change if I take this medicine? Which of these drugs is more effective?", "Will this intervention help me intervention?". The correct formulation of the clinical question is the first and very important step decision-making. On the one hand, it should exhaustively describe the specific clinical situation, on the other hand, it should be formulated in such a way that it is easy to create a strategy to search for studies in bibliographic databases.

The difference in approach in the use of information sources in "conventional" medicine and evidence based medicine can be illustrated by a simple example.

***Example 11.1.***

*A patient, N., is scheduled for an emergency tooth extraction under local anaesthesia. From the medical history it is known that the patient has previously had an allergic reaction to a local anaesthetic. The dentist, being well aware of the pathogenesis of allergic reactions (the main mediator is histamine), suggested that administration of diphenhydramine (dimedrol) antihistamine 30 min before anaesthesia would prevent the development of an anaphylactic reaction. Furthermore, the doctor sought advice from an older colleague who also advised the use of an antihistamine.*

The question formulated and asked by the dentist in the example above, would be: Is the administration of diphenhydramine effective in preventing anaphylactic reactions? The wording of the question is far from optimal, reflecting the usual, non-evidence-based, decision-making in a complex clinical situation, which are not in line with evidence-based medicine.

Correctly formulated clinical questions usually contain four elements: a) the clinical situation, b) the intervention, c) the intervention to be compared, d) outcomes. In the example given, the question should have been phrased as follows: "What is the incidence of anaphylactic reactions (*outcome*) during local anaesthesia in a patient with local anaesthetic allergy (*clinical picture*) after premedication with antihistamines

(*intervention*) compared to similar patients who did not receive such premedication (*comparison intervention*)". Sometimes the question may contain fewer elements.

**Choice of information sources**

From the point of view of traditional decision-making there is nothing in terms of the traditional decision-making approach, there is nothing wrong with the clinician in the example above, however, from the perspective of evidence-based medicine, the doctor's algorithm of action was wrong. First of all, and this is a widespread mistake, the choice of medical intervention was made on the basis of the data about the pathogenesis of the disease and the mechanism of action of the drug. Unfortunately, such an approach is unacceptable in medicine due to the fact that our knowledge about the pathogenesis of diseases and the mechanism of action of drugs is often far from exhaustive and does not take into account all possible interactions between the drug and the body. This implies that a conclusion about the clinical efficacy and safety of a drug can only be made on the basis of the results of a clinical trial. There are many examples where the decision to use a particular drug solely on the basis of an understanding of its mechanism of action and the specific pathogenesis of the disease has been erroneous. For example, at first glance, the use of antihistamines in the treatment of bronchial asthma is justified by the fact that histamine is one of the main mediators of bronchospasm. But the CR showed not only low efficacy, but also the dangers of prescribing antihistamines(an extended understanding of the pathogenesis of bronchial asthma and consideration of all mechanisms of action of antihistamines explain well the facts obtained in the clinical trials).

Secondly, in the light of the principles of evidence-based medicine, the choice of medical intervention based on the opinion of a colleague does not look any better. Even assuming that a colleague is an expert in a given area of knowledge, his or her opinion ranks last in the scale of evidence (Fig. 1). This is explained by the fact that one person's opinion is always influenced by a number of subjective factors. It is known that a physician always remembers his or her first patients better. Cases in which the therapy was effective also leave a more vivid memory trace. In addition, one doctor's experience with a particular disease or with a particular drug is always quite limited and cannot be transferred to the whole patient population.

Personal clinical experience is important for the formation of hypotheses, but because of its bias and high susceptibility to distortion of results it is not very useful for quantitative assessments, although before the introduction of controlled trials, it was personal recommendations that provided the basis for pharmacotherapy. The concept of evidence-based medicine does not at all reject physician intuition, expert opinion, it

supplements them with objective information about the most effective and safest approaches to treatment.

It should be noted that if the physician in our example were to turn to a textbook for information, which would fit within the concept of "traditional medicine", this would not be considered the optimal evidence-based approach. The textbook serve as a good source of information for gaining basic knowledge (during higher education, in various courses), but because of the so-called "lag effect", information in textbooks, manuals and reference books becomes outdated before they are published.

What might be the preferred source of information for a physician practicing evidence-based medicine? First of all, it is original journal articles about the research that has been done, because they are the primary sources of information about the results of the research. In addition, the path from obtaining the results of the study to their publication in the case of a journal article is the shortest. Thus, at the present stage, evidence-based data drawn from the biomedical literature should be an essential component of the clinical decision-making process.

**Finding research results (publications).**

The next step is to look for clinical research results that can answer the clinical question. Before the widespread use of information technology, personal computers and the Internet, the only way to find these studies was to look at printed publications (journals, books, collections of articles, etc.) and bibliographies(journals, books, collections of articles, etc.) and bibliographic indexes in the library.

Nowadays, manual retrieval of information in general and research results in particular cannot be considered optimal. Firstly, the bibliographic catalogue does not always contain a section with the topic of interest. Secondly, it is impossible to browse a large number of sources in a reasonable amount of time (a few hours, a day). Thirdly, and this is crucial today, there are about 20,000 medical journals published worldwide and more than 2 million medical articles appear each year. Not many biomedical libraries have subscriptions to all journals, so a manual search would be extremely unproductive anyway.

Most often, physicians and medical scientists turn to electronic databases, such as MEDLINE (a bibliographic search engine for medical and biological information developed by the National Institutes of Medicine a bibliographic search engine developed by the US National Library of Medicine) or EMBASE, which provide

relatively rapid access to a large volume of information. Free access to MEDLINE is provided by many web servers, e.g., PubMed.

The main advantages of electronic databases include:

- ~ the ability to quickly retrieve bibliographic data on articles on a given topic, which is almost impossible to do manually;
- ~ coverage of about 70-80% of all journal publications on a topic of interest;
- ~ the ability to quickly navigate the topic of interest through abstracts;
- ~ fast retrieval and storage of data;
- ~ possibility to contact the authors of the original article.

In this example, a bibliographic search can be carried out using the following keywords: "Histamine H1 Antagonists" AND "Hypersensitivity, Immediate" AND "Anesthetics, Local" AND "Clinical Trials". As a result of these searches, no publications have been found in the MEDLINE database. MEDLINE database did not find any publications. Consequently, there is no there is no evidence to suggest that prior administration of diphenhydramine can prevent anaphylactic reactions.

**Secondary sources of evidence**

The self-evaluation algorithm described in the previous sections of this chapter is one of the best opportunities to find evidence on an issue of interest, but it is not usually feasible for practitioners.

This is because some clinical questions require analysis of dozens and sometimes hundreds of publications, which is time-consuming. In addition, sound knowledge of clinical epidemiology, statistics and computer science is needed to effectively search, evaluate and analyse publications.

Is there any reasonable alternative? The use of secondary information resources is currently considered an option.

Secondary information resources are periodical sources in paper (journals, brochures) or electronic (CDs), databases, Internet sites, where many articles have already been analysed by experienced specialists, original studies have been selected and analysed, and systematic reviews have been created based on this.

On the one hand, it minimizes bias and eliminates errors and, on the other hand, provides clinicians with evidence-based information in an accessible, concise form.

One of the best known secondary sources of evidence is the Cochrane Digital Library, which is distributed on CD-ROM and on the Internet. The database is populated by the worldwide Cochrane Collaboration of Physicians (named after the English epidemiologist A. Cochrane).

The Cochrane Collaboration of Doctors (named after the British epidemiologist A. Cochrane who first formulated the concept of meta-analysis). Today, more than 3,000 reviews have been prepared in all fields of medicine. The Cochrane Collaboration also forms a database including abstracts of publications on controlled and randomised clinical trials that meet modern standards of quality. In this way, another secondary information product is prepared, freeing the physician from the need to critically evaluate a large number of publications and presenting already "filtered" trials.

There are not many sources in Russian yet. These include “The International Journal of Medical Practice”. The journal publishes structured abstracts of key clinical and epidemiological studies with comments, clinical guidelines, articles on methodology of clinical and analytical studies, biomedical statistics.

Another important source of evidence-based information in Russian is the annual reference book "Evidence-based Medicine". This is a new translated annual reference book, published in the original ("Clinical Evidence") in the UK for the fourth year. It has been translated into all the major languages of the world and, in addition to the drug formulary, forms the basis of clinical decision-making not only for British doctors but also for many other doctors in the English-speaking countries.

# Chapter 12. Pharmacoepidemiology

*Pharmacoepidemiology* is the discipline that studies the use of medicines and their effects at the population or large group level in order to ensure the rational use of the most effective and safest medicines.

It emerged in the 1960s at the junction of the two sciences, clinical pharmacology and epidemiology, borrowing the objectives from the former and the research methods from the latter.

The interest in pharmacoepidemiological research methods is related to certain limitations in the technology of conducting randomised clinical trials to assess the efficacy and safety of medicines.

The latter generally do not involve children, pregnant women, the elderly, and often do not take into account the effects of concomitant diseases or the use of other drugs. In addition, the scope of randomised clinical trials does not allow for the identification of rare, delayed effects of medicines.

In parallel to the growing interest in drug safety, the issue of the quality of drug use has attracted public attention. In the 1960s, the first studies appeared that examined "patterns" of drug use, not only in terms of medical, but also in terms of social and economic consequences.

**Objectives of pharmacoepidemiological research.**

The need for pharmacoepidemiological studies usually arises after the registration of a medicinal product and is related to the need to determine the benefit/risk ratio of the medicinal product in actual clinical practice.

The main objectives of pharmacoepidemiological studies are:

- to clarify the perceptions of efficacy of a medicinal product obtained in randomised clinical trials;
- identification of new, previously unknown effects of the medicinal product (both beneficial and undesirable);
- assessment of the frequency (risk) of the effects identified in the population;
- to study existing 'patterns' of medicine use, both in medical practice and in society, in order to develop interventions to improve pharmacotherapy.

**Pharmacoepidemiological research methods.**

Pharmacoepidemiological studies are usually non-experimental. They may be descriptive or analytic, and they may be prospective, retrospective or single-momentary in relation to the time of study of a phenomenon.

***Descriptive studies.***

*A descriptive case study* is a report of a single clinical observation in which it is noted, for example, that a patient develops some symptoms (often unwanted) after taking a certain medication. Of all epidemiological methods, it is the least reliable as it does not allow a causal link between symptoms and medication. However, the case description is a source of scientific hypotheses and a prerequisite for further pharmacoepidemiological research.

*A case series study* is the reporting of a group of similar clinical observations (outcomes) in patients who have taken a particular medicine. The presence of a series of similar cases increases the likelihood of an event being linked to the medication in question. At the same time, the lack of a control group does not allow to confirm the validity of this association.

***Analytical studies.***

In contrast to descriptive studies, analytical studies provide a comparison group (controlled trials) that allows to identify and assess the relationship between the use of a medicinal product and certain socially significant phenomena (morbidity, mortality, development of adverse effects, etc.)

1. *Case-control studies* are retrospective. They are the most common among pharmacoepidemiological studies. In the course of them a group of patients with an already developed outcome (symptom, disease, AEs). The group of patients is compared to a control group without the outcome; and the frequency of administration of the respective drug in each group is assessed. The relative risk associated with drug exposure is assessed by determining the odds ratio.

2. *Cohort studies* are considered the 'gold standard' of epidemiological research. They consist of a selected group (cohort) of patients, using a particular treatment are followed up to the development of the outcome of interest. These studies can be prospective - cohorts are created in the present and are observed in the future ('parallel cohort study') or retrospective - cohorts are created from historical data and are followed up to the present ('historical cohort study'). The incidence and relative risk of the outcome in the treated group compared to a control group are then

assessed. These studies are the most expensive and time-consuming, requiring a large sample and usually a long follow-up period.

**Research on medicines use.**

*Evaluation of medicine use* focuses on the quantitative and qualitative aspects of medicine use in society in terms of health, social and economic consequences. Qualitative studies usually focus on high-cost or frequently used medicines, as well as on medicines with a narrow therapeutic range or groups of medicines with a high incidence of irrational prescribing.

*A medicine consumption review* is designed to analyse the appropriateness and adequacy of the use of medicines. The assessment criteria in a drug consumption review include: indications for prescribing, rationality of drug selection and regimen, need for clinical and/or laboratory monitoring of drug therapy, availability of equivalent drugs with a better safety profile. For example, a study conducted in England in 1999 surveyed more than 17,000 prescriptions for antimicrobials by dentists in 10 different regions. Amoxicillin and metronidazole were the most frequently prescribed antimicrobials in all regions, but there was considerable variation in the mode and duration of administration. However, 44% of amoxicillin prescriptions and 33% of metronidazole prescriptions did not comply with the recommendations in the UK National Formulary; 87% of phenoxymethylpenicillin prescriptions and 42% of erythromycin prescriptions also did not comply.

Drug consumption surveys/reviews provide quantitative data on the use of medicines at different levels (HCP, region, state). The concept of DDD (Defined Daily Dose), the average maintenance dose of a medicine when used for the main indication in adults, has been developed to standardise drug consumption surveys. Data on drug consumption are usually presented as the number of DDDs per 1000 inhabitants per day or the number of DDDs per inhabitants per year (for short-course drugs). For hospitals, drug consumption is calculated as the number of DDD per 100 bed-days.

Drug consumption surveys are used to identify over- or under-use of medicines. These surveys are a good tool for monitoring the effectiveness of programmes (see below) to improve the quality of drug therapy. Data on medicines consumption provide insights into the prevalence of a range of chronic diseases, production prospects and marketing priorities, and, when combined with information on treatment outcomes, are widely used in analytical studies.

*The medicines utilisation programme* (see also Chapter 14) is a long-term project consisting of several steps: a) collecting, analysing and interpreting data on medicine use, b) developing a comprehensive programme to improve medicine use (training of doctors, patient education programmes, etc.), c) monitoring the effectiveness of the interventions by re-analysing data on medicine use.

## Chapter Pharmacoeconomics

*Pharmacoeconomics* is a branch of health economics that deals with the comparative assessment of the costs (costs) and effects (outcomes) of medicines.

Pharmacoeconomics has been developed in response to rising costs of health care, including drug therapy, the emergence of new medicines that have significantly changed the course of several diseases, the emergence of radically new medical technologies that lead to an increase not only in life expectancy, but also in its quality. Thus, society, health authorities, insurance companies and patients faced the problem of optimizing the choice of methods of diagnosis and treatment, not only for this particular patient, but also for society as a whole.

The conduct of pharmacoeconomic analysis is based on a number of principles:

- to prove the merits of a medical intervention in terms of pharmacoeconomics in comparative studies;

- the total cost of compared health interventions is the sum of the costs of all the interventions (Figure 12.1), including, for example, the costs of storing, preparing, administering, etc., as well as the costs of purchasing the interventions;

- although the word pharmaco-economics is part of the term, it is concerned with the economic aspects not only of drug therapy but also of diagnostic procedures, operations and other medical interventions that lead to a patient's recovery or improvement; that is, the concept of pharmacoeconomics has now expanded beyond drug therapy;

~ pharmacoeconomics is not about finding the cheapest drugs or medical interventions, as is so often misunderstood, but about identification of diagnostic and treatment methods with best results per every ruble spent.

There are three components to the total cost: direct, indirect and intangible.

*Direct costs* are directly related to the provision of health care (cost of drug therapy; cost of hospital stay). It is in turn subdivided into:

a) variable cost, which depends on the number of patients or health services performed: cost of medicines, cost of syringes and needles, etc;

b) fixed costs, which do not depend on the number of patients, at least for a short period of time (usually 1 year): staff salaries, equipment costs, depreciation of the premises.

Figure 12.1: An example of an analysis of the total cost of therapy.

*Indirect costs* are unrelated to the provision of health care and include costs associated with the incapacity or death of a patient due to illness or medical intervention, travel costs for the patient and relatives to a health care facility, etc.

*Intangible costs* represent emotional, psychological, social consequences of an illness or medical intervention. This cost is the most difficult to measure and estimate.

Which costs are considered in a pharmacoeconomic analysis depends on the priority point of view (perspective) of the study. There are the following perspectives of a pharmacoeconomic study: 1) the patient; 2) the treatment institution; 3) the payer; 4) society.

*The "patient" perspective* takes into account direct costs, i.e. direct costs to the patient (and their relatives) that are not covered by health insurance, as well as indirect and intangible costs. The "patient" perspective can be used in assessing the impact of therapy on quality of life or the patient's participation in paying for the health services provided.

*The 'treatment facility' perspective* (hospital, polyclinic, private practitioner) considers only direct costs. It is used when selecting, for example, local anaesthetics for

inclusion in the formulary (see below) dental hospital, the purchase of new equipment, etc.

*The "payer" perspective* refers to the costs of the insurance company, the state employer. It assesses the direct and indirect costs associated with the patient's incapacity for work. The "payer" perspective can be used when employers choose the types of insurance they will present to their employees, in the case of contracts between the insurance company/employer and the treatment facility.

*Cost-benefit analysis* has the same objectives as cost-benefit analysis effectiveness. However, it is used in circumstances where the medical interventions being compared have different objectives and their outcomes differ fundamentally, for example, coronary artery bypass surgery (increased life expectancy and quality of life) and dental prosthetics (improved quality of life). Comparing fundamentally different outcomes requires a common unit of measurement, which is money. This type of analysis can be used to compare health-care programmes with limited resources, where only one of the programmes can be implemented. The positive and negative effects of the interventions being compared are expressed in monetary units, and for each intervention the difference between the monetary value of its benefit and its cost ('net benefit') is determined. Preference is given to the programme with the "net benefit", i.e. the one with the largest difference.

There are several methods of translating programme results into monetary units. The most common is the "willingness-to-pay" method, where the respondent is asked a hypothetical question about how much they are willing to pay to achieve the outcome of the programme under study. For example, how much they would be willing to pay to use a local anaesthetic gel instead of injections of local anaesthetics to remove tartar deposits.

Often, the results of a cost-benefit analysis are expressed in terms of Quality-Adjusted Life Years (QALYs), which are the number of completed years lived in perfect health.

For example, a year lived by a patient without any manifestation of disease is estimated as 1 quality-adjusted life year. At the same time, a year in which the patient has undergone haemodialysis may be estimated much lower, for example, as 0.5 years of quality life preserved.

Given that the estimation of the number of years of quality life saved, as well as other measures of usefulness, is subjective, common approaches to developing scales have not yet been developed.

# Chapter 13 Rational use of medicines. Stages of rational pharmacotherapy

As defined by WHO experts, the *rational use* of medicines requires patients to obtain medicines appropriate to their clinical situation, in doses that meet their individual needs, for an adequate period of time and at the lowest cost to them and society.

The rational treatment process consists of a number of steps:

*Stage 1: Formulation of the diagnosis*.

The more detailed the diagnosis, the easier it will be to choose the standard of care for the patient. The diagnosis is divided into main, concomitant pathological processes, stage, variant of course, complications. The main disease is not considered to be the most severe and/or prognostically unfavourable, but the most bothersome at the moment, which in most cases is the reason for seeking medical help. Factors that may significantly influence the choice are assessed at this stage, the efficacy and safety of drug therapy: gender, age, physiological condition (pregnancy, lactation), comorbidities, underlying medication, allergy history, profession, etc.

*Stage 2: definition of the treatment goals.*
*What does the doctor want to achieve with the treatment?*

After determining the goal of treatment, the physician has to decide whether it is reasonable to prescribe a medication. In dental practice, a combination of non-pharmacological and pharmacological treatment is usually used. The following types of drug therapy are used:

- urgent (relieving acute dental care emergencies)
- course maintenance therapy, which can be symptomatic - aimed at eliminating or reducing the individual symptoms of the disease (pain relief)
- pathogenetic, removing or suppressing the mechanisms of disease development (prescription of anti-inflammatory drugs, vitamins,immunocorrectors, etc.)

- etiotropic, which removes the cause of the disease (antibiotic therapy for infectious and inflammatory diseases)
- Prophylactic, which prevents the development or exacerbation of the disease (administration of vitamins and minerals in children for the prevention of dental caries, intraoperative antibiotics)
- Substitution treatment, given in case of deficiency of biologically active substances (in case of diabetes mellitus type 1)

In determining the goal of a treatment, the physician formulates the specific clinical effects by defining a treatment goal, the physician will formulate the specific clinical effects they wish to achieve (e.g., pain control using local anesthetics) and the specific pathogenetic mechanisms they wish to target (e.g., anti-inflammatory treatment of periodontal disease). In the same patient, the aim of treatment may change at different stages of the disease. The conditions of care (e.g. facility equipment, staff qualifications) also influence the choice of treatment.

*Stage 3: Choosing a drug group and a specific drug*

Many factors influence the choice of a doctor (see Table 13.1), which not only makes rational pharmacotherapy difficult but also, in some cases, impossible. There are a huge number of medicines, but only 70 (?) pharmacological groups. All medicines with the same mechanism of action and with a similar chemical structure belong to the same group. Since the active substances in a pharmacological group have the same mechanism of action, their pharmacological effects are sufficiently similar. Thus, in the first step of the selection process, it is more convenient for the physician to evaluate groups of drugs and only then, having selected the most appropriate group, proceed to the selection of a particular drug within the group, based on the same criteria: *efficacy*, *safety*, *acceptability* and *cost.*

*Efficacy.* This is the stage where the physician evaluates the medication in terms of achieving the goal of the treatment. Drugs that are not effective enough should not be considered, so efficacy is the most important selection criterion and depends on the pharmacodynamic properties of the drug (see chapter on 'General Clinical Pharmacology'). To be effective, a drug must reach the correct concentration in the blood plasma or tissues (e.g. gingiva) and the mode of administration must ensure the correct concentration of the drug for the correct length of time. In other words, the pharmacokinetic parameters of a medicine have a direct influence on the efficacy of the treatment (see the chapter on 'General Clinical Pharmacology'). It should be emphasised that the physician has no influence on the pharmacodynamics of a medicine, however, by determining the dosing regimen, formulation and duration of therapy, the physician

ensures that the correct drug concentration is maintained in the plasma and tissues of the body, thereby ensuring the efficacy and safety of the treatment. Persons receiving other medicines Some of the pharmacological effects of medicines should be considered in certain for example, drowsiness for drivers. Consideration should be given not only to possible interactions of the prescribed drug with drugs already being taken by the patient, but also to interactions with food and drinks, especially alcoholic beverages.

*Acceptability* (ease of use). A medication with as few contraindications as possible is the most convenient to use from the physician's point of view; drug and dietary interactions; available in a variety of dosage forms and dosages. The physician's knowledge of the properties of the drug and prior experience with its use is important. Both the physician and the patient find it most convenient to use medications that have good bioavailability (see the chapter on General Clinical Pharmacy).

Both the physician and the patient find it most convenient to use preparations that have good bioavailability (see chapter on General Clinical Pharmacology) when taken orally and a prolonged effect that allows them to be used once or twice a day. It is more convenient to use preparations that do not require special storage conditions.

*The cost of treatment*. This is an important factor in deciding on treatment, whether it is financed by the state, an insurance company or the patient. From two medicines of approximately equal efficacy and safety, the cheaper one is chosen. The cost per dose or package is not counted, however, but the cost per course of treatment. The cost of treatment also includes the cost of consumables (syringes, drips, bandages, etc.), professional medical services, and resources required for coadministration (solvents, adrenaline), drugs used for elimination of undesired effects developed. The cost of treatment also includes costs of laboratory tests, the cost of treatment also includes the costs of laboratory tests to monitor the efficacy and safety of the treatment. In some cases, the use of an inexpensive but less effective and/or safer medication will lead to longer periods of treatment, increased chronicity, longer periods of disability or disability, and ultimately, higher costs (see also Chapter 5).

*Stage 4: Prescribing* - in accordance with current prescribing guidelines.

*Stage 5: Informing the patient.*

The patient should be informed about all the different treatments and helped to decide which is best for them. The patient needs to know whythe medicine is prescribed, what changes will occur and how soon the course of the disease will change after treatment begins. What will be the consequences of not taking the treatment and not taking the medicine correctly? What adverse effects are possible, how can they be prevented and what should be done if they do occur? The doctor should explain how the

medicine should be taken, how it should be stored, when the patient has to go to the doctor for another appointment and what information the patient has to prepare for the doctor. When you have finished your instructions, make sure that the patient has understood everything and ask them to repeat the most important information. If these simple rules are followed they improve the cooperation between the doctor and the patient and significantly increase the effectiveness of the treatment.

*Stage 6: Monitoring the treatment.*

If prolonged drug therapy is necessary, the treatment process should be constantly monitored by a physician, both to assess its effectiveness and to detect adverse drug reactions as early as possible. If the treatment has no effect, the diagnosis and the aim of the treatment must be verified. The correct choice of drug and its dosage regimen should be checked, as well as whether the patient is following the recommendations given to him/her for taking the medication. When the reasons for the failure have been determined, adjustments to the treatment are made. If any adverse events occur, depending on their severity, if symptoms are not life-threatening and continued treatment is necessary, a replacement may be given or a "cover treatment" may be prescribed. When the desired effect is achieved, the drugs are discontinued or maintenance doses are prescribed.

In conclusion, the rational use of drugs requires the physician to be aware of the possible positive and negative clinical aspects of drug use. It is this - the medicine in the clinical setting - that is the subject of clinical pharmacology.

# Chapter 14. Drug formulary.

In the context of rising health care costs, one of the most effective mechanisms for ensuring patient access to modern and affordable treatment is the formulary system, which aims to optimise treatment in conjunction with the control of pharmaceutical costs.

*The formulary system* is a set of organisational measures for the selection of medicines that cover patients' needs for the most effective and least costly drug therapy. In essence, the system serves as an organisational framework for putting into practice the advances in pharmacoepidemiology and pharmacoeconomics.

The introduction and use of the formulary system allows:

- ~ simplify the process of drug provision and reduce drug costs;
- ~ increase the availability of quality medicines;
- ~ improve knowledge about medicines;
- ~ optimize pharmacotherapy;
- ~ to create and update standards of drug therapy in the health-care facility.

The components of the formulary system are: formulary committee, formulary list and formulary reference book, having federal, regional and local levels. The structure of the formulary system is shown in Figure 14.1.

*A formulary committee* is a working group of specialists who organise and monitor the formulary system. The tasks of the formulary committee include analysing the use of medicinal products in a health care facility, developing and periodically updating the formulary in accordance with current recommendations, to identify needs for professional development programmes and to assist in the development of information in the field of pharmaceutical therapy.

*A formulary* is a list of formularies supplemented with basic information on listed medicines: indications, contraindications, indications, contraindications, dosages, rules of administration. The development of the formulary should include an analysis of the pattern of morbidity, collection of evidence-based data on the most clinically and cost-

effective and safe drugs and regimens and a study of consumption and costs of treatment courses.

Two approaches are commonly used as a basis for studying current drug use patterns: ABC analysis and VEN analysis. In the first, medicines are classified into 3 classes. Class A consists of 10-20% of medicines, on which 70-80% of funds are spent. Class B consists of medications with an average consumption rate. Class C consists of most medicines with low frequency of use, which together account for 25% or less of expenditure.

The VEN analysis also identifies three groups of pharmaceuticals. The first includes *Vital* medicines - medicines that are important to save life, have a life-threatening withdrawal syndrome or are permanently needed to sustain life. The second group is *Essential* - medicines that are effective in treating less serious but serious illnesses. The third group is the "Non-essential" drugs. *Non-essential medicines* are medicines for mild illnesses, medicines of questionable efficacy, and expensive medicines with symptomatic indications. The advantages of the VEN- and ABC-analysis methods are simplicity, clarity and low cost.

When deciding on the inclusion of a medicine in the formulary, in addition to financial possibilities, many parameters are taken into account, but the main ones influencing the decision of the formulary committee are efficacy and safety of the medicine.

In addition to the above-mentioned characteristics, the convenience of use is also taken into account, synergies with preparations of the same class and availability of different dosage forms, stability after dilution. As one of the main objectives of the formulary is to optimise treatment, the potential clinical efficacy of the medicinal products should take precedence over the other parameters considered.

The final conclusion should be based on data from clinical and pharmacoeconomic studies (see above) and practice guidelines. A treatment provider's formulary is usually a list of 100-200 medicines that have been approved by a formulary committee and are of a restrictive nature. A doctor can only prescribe medicines that are on the formulary. The formulary committee determines the procedure for ordering medicines that are not on the formulary. This procedure can be as simple as filling in an order form, or it can require documentation of the ineffectiveness of the previous treatment with the products on the formulary.

After approval of the formulary, the formulary committee continues to meet regularly and may revise, replace or add medicines in accordance with newly available

information. Members of the formulary committee develop recommendations for rational pharmacotherapy of diseases (treatment standards), participate in the collection and provision of medical and pharmaceutical information.

Pharmaceutical information and determine the need for education and training programmes for the staff of the health care facility on the use of medicines. The formulary system provides for regular updating of treatment standards, development of programmes for assessing the use of medicines, monitoring undesirable effects of medicines and updating the formulary list, the reference book. The use of electronic formularies, which are updated as new information about medicines becomes available or as recommendations for treatment of diseases are published, is promising.

The electronic formulary allows for rapid clarification and supplementation of the content of individual articles and sections.

The Formulary system provides the most rational clinically and cost-effective approach to the choice of medicines, facilitates the work of practitioners, improves the quality of treatment and reduces complications of pharmacotherapy, as well as reduces the patient's hospital stay and the likelihood of repeated hospital admissions.

# Section 2 Clinical pharmacology of selected groups of drugs.

## Chapter 16. Drugs for general anaesthesia.

Anaesthesia (general anaesthesia) refers to artificially induced deep sleep (controlled and reversible loss of sensation and consciousness) with analgesia, amnesia, suppression of autonomic reflexes and skeletal muscle relaxation. Depending on the drug used and its dosing regime, the severity of these effects may vary, which is used in different clinical situations and is determined primarily by the extent and duration of the planned surgical intervention. The required depth of anaesthesia is monitored by reflexes, muscle tone, cardiovascular and respiratory system reactions.

In modern anaesthesiology the most commonly used combination of anaesthetics with narcotic analgesics, benzodiazepines, neuroleptics, neuroleptics, muscle relaxants, which allows for a quick and smooth induction into anaesthesia, sufficiently rapid recovery from it, achieving adequate pain relief (sometimes with preserved consciousness) with the smallest possible risk of undesirable effects.

*Anaesthetic agents* are chemical compounds of different classes, which act on different neurons in a similar way, resulting in their inhibition.

**Indications for use in dentistry**:

- ~ general anaesthesia in the inpatient phase (most common);
- ~ in out-patients (max. 1 %) in cases of inability to apply local anaesthetics in children, patients with intolerance to all local anaesthetics, CNS malformations and mental diseases, emergency interventions for widespread infections and in the case of an emergency intervention for widespread infections and inflammations of the maxillofacial region.

*Classification.* Depending on the route of administration, general anaesthetics are divided into two groups, inhalational anaesthetics and noninhalational anaesthetics(Table 16.1)

**Table 16.1: Classification of general anaesthetics by route of administration.**

| Inhalational | Non-inhalational |
|---|---|
| *Gaseous substances:* | *Barbiturates:* |

| | |
|---|---|
| dinitrogen oxide (nitrous oxide)<br>*Liquid volatile substances:*<br>Halothane (narcotan, fluorothane)<br>isoflurane (foran)<br>enflurane (etran)<br>Diethyl ether (anaesthetic ether)* | Thiopental sodium (thiopental)<br>hexobarbital (hexenal)<br>*Derivatives of various compounds*:<br>Ketamine (calypsol, ketamine)<br>propofol (diprivan, propofol) |

* Diethyl ether is only of historical interest today, as modern general anaesthetics are much safer and better controlled.

The mechanism of action of general anaesthetics is not fully understood. Most of their clinical effects are based on their ability to inhibit inter-neuronal transmission in the CNS. They are known to alter the permeability of ion channels, increase the excitation threshold of cells, and inhibit spontaneous and stimulated neuronal activity. Inhalational anaesthetics increase the excitability threshold by activating potassium currents. A number of noninhalational anaesthetics, particularly barbiturates, interact with GABA-benzodiazepine-barbiturate receptor complex, potentiating the effects of GABA.

**Main therapeutic effects**

The sensitivity of different neurons to general anaesthetics varies and is directly related to the dose of the drug. At low concentrations, anaesthetic agents act on cells in the dorsal horns of the spinal cord, interrupting sensory transmission, including that of pain, through the spinothalamic tract. At higher concentrations, anaesthetic agents act on cells in the reticular formation, leading to suppression of its activating function and development of the surgical stage of anaesthesia. Further increasing the concentration of anaesthetic agents is accompanied by depression of the respiratory and vasomotor centres of the medulla oblongata.

The traditionally distinguished stages of anesthesia*: analgesia, agitation, surgical anesthesia* and *depression (paralysis) of the medulla oblongata* were described many years ago by observing the action of the first general anesthetic that entered into clinical practice - diethyl ether. With modern methods of anaesthesia, the first and second stages are often not clinically apparent. Reliable signs of the onset of surgical anaesthesia are inhibition of the corneal reflex while respiration remains regular in frequency and depth.

**Pharmacokinetics.**

*A. Inhalation anesthetics.*

The depth of anesthesia is directly dependent on the content of inhalation anesthetic in the brain tissue. In turn, the entry of drugs into the brain tissue and maintaining their concentration at a constant level depends on the partial pressure (voltage) of the agent in the blood. The partial pressure of an inhalation anesthetic in the arterial blood is determined by a number of factors, among which are:

- ~ *The solubility of a substance in the blood*, an indicator of which is the "blood / gas distribution coefficient", which reflects the ratio of the concentrations of the drug in the blood and in the gas phase at equilibrium, i.e. at equal partial pressure. The higher this coefficient (and the better the drug dissolves in the blood), the more it is needed to create a partial pressure that ensures the achievement and maintenance of the desired concentration of inhalation anesthetic in the brain tissue. In other words, there is an inverse relationship between the solubility of the drug and its partial pressure in the blood.
- ~ *The concentration of the drug in the inhaled air*. An increase in the content of anesthetic in the inhaled air leads to an increase in its entry into the blood. Anesthetics that are moderately soluble in blood (halothane, isoflurane, enflurane) begin to act relatively slowly and are used in higher concentrations to speed up anesthesia than to maintain anesthesia. For example, the initial concentration of halothane in the inhaled mixture is 3-4 vol. %, and supporting - 1-2 vol. %.
- ~ *Pulmonary ventilation*. The partial pressure of an inhalation anesthetic in the blood is proportional to lung ventilation. For poorly soluble substances in the blood, this dependence is less pronounced than for well and moderately soluble substances. Forced hyperventilation increases the rate of development of anesthesia, and respiratory depression, for example, narcotic analgesics, slows down the onset of anesthesia. This is especially important in outpatient settings in the absence of artificial ventilation.
- ~ *Pulmonary blood flow.* An increase in cardiac output and an increase in pulmonary blood flow reduce the partial pressure of moderately and well soluble anesthetics, with little effect on the blood levels of poorly soluble drugs. A decrease in pulmonary blood flow leads to an increase in the partial pressure of anesthetics in the blood and an acceleration of the induction of anesthesia.
- ~ *Arteriovenous gradient of anaesthetic concentration.* Tissue uptake of the anaesthetic reduces its concentration in the venous blood and increases the

arteriovenous gradient. The larger the gradient, the longer it takes to reach a stable plasma concentration of the drug. Tissues with high perfusion (brain, heart, liver, kidneys) are more affected by anaesthetic partial pressure and anaesthetic induction time. Poorly perfused tissues (adipose tissue, muscle, skin) accumulate anaesthetics slowly and have less effect on the rate of onset of anaesthesia. Depending on their chemical and physico-chemical properties, inhalation anaesthetics have a different affinity for different tissues, which is described by the "tissue/blood distribution coefficient".

The efficacy of an inhaled anaesthetic and its dose dependence can be assessed using a conventional value, *the minimum alveolar concentration* (MAC). MAC refers to the concentration (percentage of anaesthetic in the alveolar gas mixture) at which half of patients achieve no response to the damaging factor. The weaker the anaesthetic effect of the drug, the higher the concentration. For example, even breathing pure dinitrogen oxide does not allow half of the patients to achieve no reaction to the injury (i.e. even the anesthetic concentration in the breathing mixture equal to 100 vol.% is less than the MAC for dinitrogen oxide). The introduction of this criterion has made it possible to quantify the effect of a number of factors on anaesthesia. MAC decreases with age, when narcotic analgesics, sedatives, and hypnotics are prescribed, and hence in these cases the dose of inhaled anesthetics should be reduced. The main pharmacokinetic characteristics of inhalational anaesthetics are presented in Table 16.2.

**Table 16.2 Pharmacokinetic characteristics of inhaled anaesthetics**.

| Anaesthetic | Coefficient distribution blood/gas | Coefficient of distribution brain/blood* | MAC (vol. %) |
|---|---|---|---|
| Dinitrogen oxide | 0,47 | 1,1 | >100** |
| Halothane | 2,30 | 2,9 | 0,75 |
| Isoflurane | 1,40 | 2,6 | 1,40 |
| Enflurane | 1,80 | 1,4 | 1,68 |

* Ratio of anaesthetic content in brain tissue to blood (reflects the affinity of the anaesthetic for brain tissue);

**- exceeding the MAC of 100 vol. %, which in reality cannot be, indicates that

The presence of dinitrogen oxide at the concentration being used will result in very little anesthetic activity.

Once the inhaled anaesthetic is discontinued with the inhaled mixture, its concentration in the brain progressively decreases and the patient emerges from

anaesthesia. The rate of exit is influenced by the same factors that influence the induction and maintenance of anaesthesia. Inhalation anaesthetics that are poorly soluble in blood are eliminated from the body more rapidly than those that are well soluble. The longer the duration of anaesthesia, the slower the partial pressure of the anaesthetic agent decreases due to the fraction of the anaesthetic that has accumulated in the tissues, and the longer it takes for the patient to emerge from anaesthesia.

Most inhaled anaesthetics are excreted through the lungs with the exhaled air, but the liver's enzyme systems also take part in their metabolism. For example, up to 15-20% of halothane is metabolized in the liver to form trifluoroacetic acid, bromine ions and chlorine. Under hypoxic conditions free radical formation of chlorotrifluoroethyl is possible, which has hepatotoxic effect. Up to 2-3% enflurane also undergoes hepatic metabolism with the formation of small amounts of difluoromethoxyfluoroacetic acid and fluorine ions. Metabolites are excreted by the kidneys. Dinitrogen oxide is not metabolized in the human body.

*B. Noninhalational anaesthetics*

The rapid onset of effects of noninhalational anaesthetics is due to their lipophilicity (thiopental sodium, ketamine) or to their rapid acquisition of lipophilic properties in plasma (hexenal). Soluble in fat, they readily penetrate the blood-brain barrier and create high concentrations in the CNS. Their rapid redistribution to other, less well supplied tissues determines the short duration of the effect. Most noninhalational anaesthetics bind little to plasma proteins, except sodium thiopental, which has a 75% binding effect. The latter requires rapid administration of the initial dose in order to achieve high concentrations of the free drug fraction and rapid induction of anaesthesia.

All drugs in this group are metabolised by the liver and the metabolites are excreted by the kidneys. The slow metabolism of sodium thiopental and its ability to be deposited in adipose tissue and muscle causes easy cumulation, which is accompanied by prolonged anaesthesia, the development of adverse effects and is a serious complication of the postoperative period. The water-soluble phenol propofol does not cumulate with repeated injections or prolonged infusion.

**Undesirable effects**

A. *Inhalational anaesthetics*

To a greater or lesser extent, all inhalational anaesthetics have systemic effects that are least pronounced with dinitrogen oxide. However, in certain clinical situations cardiodepressant and several other adverse effects of this anaesthetic may develop.

Volatile liquid anaesthetics (Table 16.3) reduce BP, but whereas with halothane and, to a lesser extent, enflurane, this is due to a decrease in cardiac output (a significant decrease in myocardial contractility), isoflurane causes a decrease in ROS (its cardiodepressant effect is less pronounced). The decrease in myocardial contractility is proportional to the dose of anaesthetic. The stimulating effects of surgery and hypercapnia reduce the cardiodepressant effect of these drugs. Halothane causes bradycardia, enflurane has a less pronounced effect and isoflurane causes tachycardia.

Dinitrogen oxide has the least potent cardiovascular effects, causing sympathetic stimulation which can reduce the cardiodepressant effects of the other anaesthetics. Thus, the combination of halothane and dinitrogen oxide causes less myocardial depression than anaesthesia with halothane alone.

Halothane sensitizes the myocardium to the effects of catecholamines, which may result in ventricular arrhythmias, particularly in patients with CHD, when used in combination with sympathomimetics or when catecholamine levels are initially elevated, e.g. in patients with pheochromocytoma.

**Table 16.3 Undesirable effects of inhaled anaesthetics - volatile liquids.**

| | Effects | Halothane | Enflurane | Isoflurane |
|---|---|---|---|---|
| | Cardiovascular system: | | | |
| ↑ | Cardiac output | + | + | |
| ↓ | OPPS | | | + |
| ↑ | Cerebral blood flow | + | + | + |
| | Bradycardia | + | | |
| | Tachycardia | | | + |
| ↓ | Myocardial contractility, | + | + | + |
| ↑ | myocardial pressure in right atrium | | | |

| | | | |
|---|---|---|---|
| CNS:<br>signs of seizure activity on EEG | | At high concentrations | |
| Respiratory system:<br>↑ Respiratory frequencies<br>↓ Respiratory volume<br>Bronchospasm<br>↓ Mucociliary transport<br>Irritant effect on airways<br>Short-term respiratory cessation<br>Laryngospasm | +<br>+<br><br>+ | +<br>+<br>+<br>+<br>+<br>+<br>+ | +<br>+<br><br>+<br>+<br><br>+ |
| Kidneys:<br>↑ Renal vascular resistance<br>↓ Renal blood flow<br>↓ Glomerular filtration rate | +<br>+<br>+ | +<br>+<br>+ | +<br>+<br>+ |
| Liver:<br>↓ Hepatic blood flow | + | + | + |

Inhaled anaesthetics reduce cerebral vascular resistance and increase cerebral blood flow and intracranial pressure. This effect is most pronounced with halothane and least pronounced with dinitrogen oxide.

In contrast to dinitrogen oxide, other inhalation anaesthetics reduce respiratory volume and increase respiratory rate, resulting in decreased pulmonary ventilation and increased partial pressure of carbon dioxide. This effect is most pronounced with isoflurane and enflurane. Ventilatory support balances out the negative effects of the inhaled anaesthetic on breathing Mucus builds up in the airways if anaesthesia is prolonged (danger of atelectasis and pneumonia). Enflurane and isoflurane irritate the airways. This can cause temporary respiratory distress with delayed induction of anaesthesia and laryngospasm with the latter.

Inhaled anaesthetics adversely affect hepatic and renal blood flow.

Inhalation anaesthetics can cause a number of universal syndromes, which are a serious complication of their use:

*Malignant hyperthermia*. Rarely observed genetically determined hypermetabolic syndrome (catabolism in muscles), manifested by hyperthermia, muscle rigidity that develops despite the use of muscle relaxants - and tachycardia, arterial hypertension and hypothyroidism, acidosis, hyperkalemia, myoglobinuria, oliguria. Treatment includes immediate discontinuation of the anaesthetic (change of agent, anaesthetic device and completion of the operation as soon as possible) and symptomatic treatment (control of hyperthermia, acidosis, electrolyte disturbances, etc.). A specific agent is a blocker of calcium release from the sarcoplasmic reticulum - dantrolene, which is currently not registered in our country, forcing the use of symptomatic drugs.

*Hepatotoxicity*. Liver complications are observed in 1 out of 35000-40000 incidence of acute liver necrosis is 1 in 250,000-300,000 cases of halothane anaesthesia. However, studies which have analysed a large amount of clinical material, particularly in the US National Halothane Study, have not shown a higher incidence of liver damage with halothane compared to other inhalation anaesthetics. It is likely that hepatotoxic effects occur in patients with a genetic defect in hepatocyte membrane, making them susceptible to the damaging effects of halothane.

Risk factors for hepatotoxic effects:

- a history of liver disease;
- fever, jaundice, transient increase in liver enzyme activity, observed during previous anaesthesia with halothane;
- reuse of halothane less than 3 months after previous use.

*Nephrotoxicity*. Inorganic fluorine released during biotransformation of fluorine-containing anesthetics when reaching a concentration of 50 μmol/L and higher can cause renal damage with acute renal failure. Although nephrotoxic effects have only been described following methoxyflurane anaesthesia, patients with a history of renal disease are at risk for all fluoroablative anaesthetics.

*Haematotoxicity.* During prolonged exposure to dinitrogen oxide under insufficient ventilation, the development of megaloblastic anaemia has been described, in particular in operating theatre workers (oxidation by dinitrogen oxide of cobalt in the cyanocobalamin molecule).

*B. Non-inhalation anesthetics*

*Dyspeptic syndrome* in the form of nausea, less often - vomiting can develop with the use of any non-inhalation agent for anesthesia (propofol is the least frequently cited cause of nausea and vomiting). Developed during the period of awakening, the dyspeptic syndrome is often combined with headache.

*Suppression of the respiratory and vasomotor centres* up to apnoea and collapse is most common in overdose of non-inhalational anaesthetics. However, even in therapeutic doses barbiturates depress the respiratory and vasomotor centres, and decreases stroke and cardiac output and BP, while propofol decreases HRV, HR, cardiac output and BP and can cause bradycardia and short-term apnoea.

*Local irritant effect* with development of tissue damage at the injection site, phlebitis, thrombosis, thrombophlebitis are most common with sodium thiopental and propofol.

*Bronchospastic syndrome* may develop during or after anaesthesia with sodium thiopental, propofol.

*Allergic reactions up* to and including anaphylaxis are most common with hexobarbital, propofol.

Barbiturates and propofol cause *excitation of the vagus nerve*.

Ketamine administration is associated with *increased sympathetic activity*, manifested by increased plasma levels of adrenaline and noradrenaline, increased HR, cardiac output and some rise in BP. *Chewing muscle spasm* and *salivation* may occur. Involuntary muscle twitching may occur.

Ketamine increases cerebral oxygen demand and cerebral blood flow; therefore it should not be used in patients with increased intracranial pressure. Ketamine can lead to disorientation, hallucinations, nightmares and, in the longer term, depression. Premedication with benzodiazepines reduces the severity of these effects.

In doses higher than those recommended, propofol can inhibit the synthesis of adrenal cortex hormones.

Laryngospasm, excessive mucus secretion, decreased hepatic blood flow and glomerular filtration are possible during sodium thiopental administration.

**Drug interactions**

Despite the same mechanism of action and similar pharmacodynamic effects, general anaesthetics interact differently with individual drugs. These interactions may occur both during and after anaesthesia.

A. *Inhalational anaesthetics* - see Table 16.4.

**Table 16.4 Drug interactions of inhalational anaesthetics**

| Anaesthetic | Drug | Effect |
|---|---|---|
| Halothane | Tricyclic antidepressants | Risk of arrhythmia |
| | Cardiac glycosides | Risk of bradycardia |
| | Aminoglycosides, lincomycin | Increased neu blockage (risk of apnoea) |
| | Theophylline, adreno- and sympathomimetics, including risk of anorexics | Risk of arrhythmia |
| Isoflurane | Dihydropyridine antagonists of calcium | Risk of arterial hyp |
| Enflurane | Isoniazid | Risk of nephrotoxi |
| Halothane, isoflurane, enflurane | Tricyclic antidepressants, ACE inhibitors, beta-adrenoblockers, verapamil | Risk of arterial hyp |
| | Anxiolytics, neuroleptics | Risk of arterial hyp Increasing depress on the CNS |
| | Vancomycin | Increased ri hypersensitivity reactions |
| | Oxytocin | Reduced effect of Risk of arterial and arrhythmias |
| Halothane, possible, isoflurane and enflurane | Isoniazid | Increased hepatoto |
| Isoflurane, enflurane | Non-depolarising myorelaxants | Increasing the myorelaxants |
| Halothane, enflurane | Verapamil | Risk of A-B blocka |

B. *Non-inhaled anaesthetics*.

*Thiopental sodium.* When combined with other anesthetics, antidepressants, anticonvulsants, sedatives, hypnotics, opioid analgesics, the sedative, cardiodepressant, hypotensive effect is increased and the risk of respiratory depression increases. In combination with hypotensive drugs, the risk of hypotension increases.

*Hexobarbital*. When used concomitantly with other CNS depressants (as other barbiturates), there may be a significant summation of the depressant effect on the CNS.

*Ketamine*. Increases myorelaxation induced by tubocurarine and dithyline. In patients receiving iodine-containing medications and thyroid hormones, increase the risk of arterial hypertension and tachycardia.

*Propofol*. HR-lowering drugs increase the risk of marked bradycardia, opioid analgesics increase the risk of apnoea. Pharmaceutically incompatible with infusion solutions of other drugs.

**Clinical features of anaesthetics**

A. *Inhalational anaesthetics*

In addition to their ability to induce anaesthesia, general anaesthetics have several other properties that can be used therapeutically. For example, halothane induces bronchodilation, which is used for life-threatening attacks of bronchial asthma. Halothane, isoflurane, enflurane cause relaxation of the uterine muscles, while dihydrogen oxide has no effect on their tone.

However, more often additional properties of anaesthetics serve as contraindications for their use (Table 16.5).

**Table 16.5 Contraindications to the use of inhalational anaesthetics**

| Anaesthetic | Contraindication |
|---|---|
| All | Individual intolerance to the drug anamnesis |
| Halothane | Abnormal liver function,<br>History of malignant hyperthermia,<br>pheochromocytoma, thyrotoxicosis,<br>hypercatecholaminaemia,<br>myasthenia gravis, |

| | |
|---|---|
| | intracranial hypertension, porphyria |
| Enflurane | history of seizures, porphyria |
| Dinitrogen oxide | Hypoxia, diseases of the nervo system, Chronic alcoholism, state of alcol intoxication |

Inhaled anaesthetics should be used with particular caution in patients risk groups:

- ~ Age above 60 years of age.
- ~ Hepatic and renal disease.
- ~ Porphyria.
- ~ Epilepsy or history of seizures.
- ~ Rhythm and conduction disorders.
- ~ Congestive heart failure.
- ~ Hypovolemia.
- ~ Cerebral trauma, intracranial tumours, increased intracranial pressure.
- ~ COPD, pulmonary emphysema.
- ~ The use of drugs with which general anaesthetics interact.
- ~ Risk factors for hepatotoxic effects (see above).
- ~ Vitamin B12 deficiency (when using dinitrogen oxide).

*Use in pregnancy*. For pregnant women who have undergone surgery and anaesthesia for a concomitant medical condition, there is an increased risk of abortion, but it is unclear if this is due to the disease, the surgery, anesthesia or a combination of all factors.

Halothane is contraindicated in the first trimester and during labour. Enflurane is contraindicated throughout pregnancy. Isoflurane should not be used for abortion (danger of increasing bleeding).

In the third trimester, inhaled anaesthetics can cause respiratory depression in the neonate. Dinitrogen oxide inhibits B12-dependent enzymes involved in DNA synthesis and should be used with caution in pregnant women.

*Use in lactation*. Enflurane is contraindicated during lactation. Halothane passes into the mother's milk, but there are no direct indications that it should not be used during lactation. Dinitrogen oxide, halothane, enflurane, isoflurane in children can be used if breathing rate, pulse rate, BP and reflexes are closely monitored.

B. *Nenal anaesthetics*

When anaesthetics is administered intravenously, anaesthesia develops very rapidly and is of short duration. Therefore, non-nhalational anaesthetics are used for short-term procedures, as anaesthetics for induction or in combination with inhalational anaesthetics for longer procedures.

Some of these drugs, e.g. barbiturates, propofol induce deep sleep by depressing consciousness, but do not have an analgesic effect of their own. The barbiturates cause a distinct muscle relaxation. They, especially sodium thiopental, have expressed anticonvulsant activity and ability to decrease metabolism in brain cells, their glucose and oxygen consumption.

**Table 16.6 Contraindications to the use of non-inhaled anaesthetics.**

| Anaesthetic | Contraindications |
|---|---|
| All | Individual intolerance |
| Thiopental sodium | Airway obstruction,<br>Oropharyngeal inflammation oedema (phlegmon of the oral cavi pharyngeal space), neck,<br>Ethanol intoxication,<br>Malignant hypertension,<br>Lactation, Porphyria |
| Hexobarbital | Liver and renal impairment,<br>Sepsis and febrile syndrome,<br>Inflammatory diseases nasopharynx,<br>Respiratory failure,<br>Heart failure, Intestinal obstruct<br>Caesarean section (foetal asphy |
| Ketamine | Increased intracranial (including cerebral stroke),<br>Epilepsy, pre-eclampsia, eclam history seizures in anamnesis,<br>Chronic alcoholism,<br>Arterial hypertension,<br>Severe heart failure,<br>Angina pectoris or myocardial i within the last 6 months,<br>Severe renal insufficiency, |

| | |
|---|---|
| | Laryngeal and pharyngeal surge |
| Propofol | Under 3 years of age,<br>Pregnancy, lactation |

With extreme caution and in lower doses, ketamine and barbiturates are used in

In high-risk patients (Table 16.7), special care should be taken to use ketamine and barbiturates in lower doses.

**Table 16.7 Risk factors for adverse events**

| Anaesthetic | Risk factor |
|---|---|
| Topental Sodium | Hepatic and renal insufficiency,<br>Arterial hypotension,<br>Heart failure,<br>Arterial hypotension, hypovolemia,<br>Bronchoobstructive disorders,<br>Addison's disease,<br>Diabetes mellitus,<br>Myxedema,<br>Myasthenia gravis,<br>Anaemia,<br>Elderly and debilitated patients,<br>Febrile syndrome,<br>Inflammatory diseases o nasopharynx,<br>Chronic alcoholism,<br>Obesity, Cachexia,<br>Hypoproteinemia (along wi reduction, a slower drug infusion s used.),<br>Administration of drugs wit thiopental interacts.<br>Pregnancy, young age. |
| Hexobarbital | Cardiovascular disease,<br>Young age,<br>Frail patients |

| | |
|---|---|
| Ketamine | Renal dysfunction,<br>Cardiac insufficiency |
| Propofol | Old age,<br>Cardiovascular disease,<br>Hypovolemia,<br>Epilepsy,<br>Respiratory system disorders,<br>Liver and kidney abnormalities,<br>Disorders of lipid metabolism |

Other non-inhalational anaesthetics, such as ketamine, cause somatic analgesia with incomplete deprivation of consciousness, but have insufficient visceral analgesic activity. Somatic analgesia induced by ketamine develops against a background that resembles neuroleptanalgesia. There is no muscle relaxant effect and there is a subtle relaxation of the bronchial musculature. The pharyngeal and laryngeal reflexes are maintained during the anaesthesia phase (clinically it is very important that the gag reflex and cough reflex are maintained).

Cerebral blood flow and metabolism are reduced during propofol administration, intracranial and intraocular pressure. The drug has a definite antiemetic effect, so that vomiting and nausea are rare during its use. Waking up after anaesthesia is quicker and less uncomfortable than with barbiturates.

**Features of clinical use in different categories of patients**

*Use in pregnancy.*

Thiopental sodium requires special caution in pregnancy.

Although hexobarbital penetrates the placental barrier, it is contraindicated in pregnancy only in caesarean section (risk of fetal asphyxia).

Propofol is contraindicated in obstetric practice (penetrates the placental barrier and may cause neonatal depression); can be used in the first trimester of pregnancy for medical abortion.

Any non-inhaled anaesthetic may cause respiratory depression in the neonate.

*Lactational use.*

Sodium thiopental and propofol are contraindicated in lactation.

Although there is no information about known adverse effects of ketamine on the lactating infant, it is recommended that ketamine not be administered while breastfeeding.

*Use in children.*

Thiopental sodium requires special caution when used in children.

Hexobarbital in children is used only as a 1% solution.

Propofol is contraindicated in children less than 3 years of age and is not recommended for use as a sedative in children undergoing ventilatory ventilation.

**Medications**

A. ***Inhalational anaesthetics***

*Dinitrogen oxide* (nitrous oxide) has a marked analgesic and mild anaesthetic effect, and has a high MAC. It is used in mixture with oxygen. The disadvantages of anaesthesia with dinitrogen oxide are the inability to achieve deep sleep, the presence of arousal stage, the lack of relaxation of the masticatory muscles. In doses which do not cause anaesthesia it is used for short-term, minor traumatic interventions. It is used in combination with other inhalational anaesthetics for rapid initiation of anaesthesia. It has a high safety profile but in patients with CHD and hypovolemia may be cardiodepressant. It may potentiate opioid-induced respiratory depression.

It is available in liquefied (compressed) form under pressure of 50 atm. (metal cylinders marked "N2O for medical use") in 10 litres.

*Halothane* (narcotane, fluorothane) is a fluorinated hydrocarbon, rarely causing post-operative nausea and vomiting. It inhibits secretion of salivary glands, causes relaxation of masticatory muscles, which creates favourable conditions for work of a dental surgeon in the oral cavity. It has a strong anaesthetic effect and at low concentrations has a mild anaesthetic effect. In hypercapnia, asympathomimetics and other drugs have been shown to cause a high risk of arrhythmias. Despite the ability of halothane to cause hypoventilation, it is used in patients with bronchial asthma, as it has a bronchodilator effect without irritating the airway mucosa. There is a risk of liver and kidney damage during its use.

It is available as solution for inhalation and inhalation anaesthesia (dark glass vials and dropper bottles) 50 and 250 ml each.

*Enflurane* (etran) is a fluorinated ester. Its narcotic activity is 2 times lower than that of halothane. It has similar effect to halothane on cardiovascular and respiratory system. There is a risk of seizures during its use, especially in case of hypercapnia. The risk of liver damage is less than that of halothane and there may be renal damage. Potentiates the effects of non-depolarising muscle relaxants.

Available as liquid for inhalation anaesthesia (dark glass vials) 125 and 250 ml.

*Isoflurane* (foran) is a fluorinated ester, spatial isomer of enflurane. It is intermediate between halothane and enflurane in degree of severity of narcotic effect. Its effects are fast onset and rapidly discontinued. It is less metabolized in the body, which reduces the risk of toxic effects, so the drug is recommended for use in patients with impaired hepatic and renal function. The drug has little effect on myocardial contractility and BP, but hypotensive reactions are possible when taking beta-adrenoblockers. Isoflurane has anticonvulsant effect, reduces sensitivity of brain to ischaemia and myocardium to catecholamines.

It is available as a liquid for inhalation anaesthesia (dark glass vials) of 100 ml.

***B. Nenal anaesthetics***

*Sodium thiopental* (thiopental, thiopental sodium, thiopental sodium lyophilisate for injection) is an anaesthetic of the barbiturate group without analgesic effect. Anaesthesia is carried out using 1-2.5% solutions prepared immediately prior to anaesthesia. The solution has an alkaline reaction and when injected into an artery it causes spasm and, if released into the surrounding vascular tissue, leads to necrosis.

It is used mainly in hospitals and very rarely in outpatient settings due to its low therapeutic latitude, ability to cumulate, and difficulty in dosing, high risk of adverse effects.

Sodium thiopental reduces both cerebral blood flow and cerebral metabolism, but the latter effect is stronger, which ensures its cerebro-protective effect in hypoxia. The absence of increased cerebral blood flow makes the use of sodium thiopental preferable in patients with intracranial hypertension.

The dose of the drug is selected individually, taking into account body weight, effect of premedication, concomitant diseases. Maximum dose for adults is 1.0 g. In children, thiopental sodium is used intravenously by drip, starting from the first weeks of life, and depending on age, the dose varies from 2 to 7 mg/kg of body weight.

It is available as lyophilisate, lyophilised powder and powder for preparation of solution for injection (vials) of 0.5 and 1 g.

*Hexobarbital* (hexenal) is a derivative of barbituric acid; it has hypnotic and muscle relaxant effects; after single intravenous administration, the state of anaesthesia lasts up to half an hour. It is used for injecting anaesthesia and for general anaesthesia

during short-term (not more than 15-20 minutes) surgeries, acute psychosis (including alcohol). It is administered in 1-2% (up to 2.5-5%) solution.

The highest daily dose is 1 g.

It is available as lyophilisate for preparation of solution for intravenous injection and as foam mass for preparation of injection solution (vials) of 1 g.

*Ketamine* (calypsol, ketamine) is similar in structure to hallucinogens and causes so-called 'dissociated or disassociated' anaesthesia characterised by catatonia, amnesia and analgesia. It is administered intravenously and intramuscularly. With intravenous administration, anaesthesia develops after 30-60 seconds and lasts 5-15 minutes; with intramuscular administration it takes 2-4 minutes and lasts from 12 to 25-40 minutes.

Ketamine is the only non-inhalational anaesthetic that increases sympathetic activity. After intravenous administration the maximal sympathetic stimulation is observed after 2-4 min and lasts 10-20 min.

The initial intramuscular dose is 4-8 mg/kg, maintenance dose is 3 mg/kg. When administered intravenously, the initial dose is 2-3 mg/kg, maintenance dose is 1 mg/kg bolus or 2 mg/kg/hr as an infusion.

It is available as 5% solution for injection (ampoules, vials, dark glass vials) 2, 5 and 10 ml.

*Propofol* (diprivan, pofol, recofol) is used as an emulsion administered intravenously. Like barbiturates, it has no analgesic effect. The effect develops quickly (after 30-60 min) and ends quickly (after single injection, consciousness is restored after 4 min), so the drug is widely used in outpatient practice. It is used for induction anesthesia, supporting anesthesia, for sedation during EVI (except for children), surgical and diagnostic procedures. For anaesthesia induction for most patients under 55 years of age the average dose is 1.5-2.5 mg/kg, over 55 years of age 1-1.5 mg/kg. For maintenance anaesthesia, either a continuous infusion at an average rate of 4-12 mg/kg/hour or repeated bolus injections of 25-50 mg.

## Control questions

1. Which statement regarding general anaesthetics is incorrect?

a) general anaesthetics inhibit spontaneous and stimulated neuronal activity.
b) the sensitivity of different neurons to anaesthetics is dose-dependent.
c) the depth of anesthesia depends on the concentration of the anesthetic in brain tissue.
d) the concentration of anaesthetic in blood is inversely proportional to its concentration in brain tissue
e) an overdose of anaesthetics develops respiratory depression.

2. Specify the anaesthetic with analgesic properties:

a) thiopental sodium.
b) ketamine.
c) propofol.
d) hexobarbital.
e) all of the above anaesthetics.

3. Which anaesthetic has arrhythmogenic undesirable effects?

a) halothane.
b) thiopental sodium.
c) isoflurane.
d) dinitrogen oxide.
e) propofol.

4. The partial pressure of an inhaled anaesthetic in the blood is affected by all factors except:

a) blood solubility of the anaesthetic.
b) pulmonary ventilation.
c) the concentration of the anaesthetic in the inhaled gas mixture.
d) lipophilicity of the anesthetic.
e) pulmonary blood flow.

5. Which effect is not characteristic of the action of halothane?

a) bradycardia.
b) increased myocardial sensitivity to catecholamines.
c) decreased cardiac output.
d) sympathetic stimulation.
e) increased cerebral blood flow.

6. The risk of developing hypotension during general anaesthesia is increased in patients taking:

a) beta-adrenoblockers.
b) ACE inhibitors.
c) tricyclic antidepressants.
d) anxiolytics.
e) any of the following.

7. Which of the undesirable effects is characteristic of ketamine?

a) laryngospasm.
b) cardiodepression.
c) hallucinations.
d) arrhythmias.
e) histamine release.

8. Which of the volatile fluid anaesthetics can be used in a patient with chronic hepatitis?

a) halothane.
b) isoflurane.
c) enflurane.
d) none of these.
e) any of these.

9. What is a contraindication for the use of sodium thiopental?

a) phlegmon of the floor of the mouth.
b) porphyria.
c) inability to administer intravenously.
d) all of the above.
e) none of the above.

10. What is not characteristic for propofol?

a) contraindicated in pregnancy and lactation.
b) rarely causes nausea and vomiting.
c) does not have a cumulative effect.
d) requires dose reduction in patients over 55 years of age.
e) has a long-lasting effect.

## Chapter 17. Local anaesthetic agents

*Local anaesthesia* is anaesthesia without stunning the patient. The effect is on the peripheral mechanisms of pain stimulus perception and on the transmission of the pain impulse. During infiltration and application (surface, terminal) anesthesia affect the peripheral receptors, with conductive anesthesia blocks the pain impulse along the nerve trunk.

*Local anaesthetics* are drugs that reversibly block the generation and conduction of the pain impulse along nerve fibres.

In dental practice, local anaesthetics are applied or injected. The properties that a local anaesthetic must have are:

- ~ the ability to provide effective anaesthesia;
- ~ short latency period (rapid development of anaesthetic effect);
- ~ sufficient duration of the analgesic effect corresponding to the duration of the intervention;
- ~ no irritating and damaging effect on nerve elements and surrounding tissues;
- ~ absence of systemic toxicity;
- ~ absence of local vasodilatory effect;
- ~ water solubility;
- ~ stability during storage and sterilization.

It should be stressed at once that there is no single drug today that fully complies with these requirements.

### The indications for use in dentistry

Indications for use in dentistry:

- ~ any oral or facial intervention accompanied by pain (applicative, infiltrative and conduction anaesthesia);
- ~ anaesthesia of dental hard tissue, mucous membranes, wound surfaces (in the form of applications).

*Chemical properties*. Local anaesthetics are weak bases, soluble in fat and poorly soluble in water. For clinical use they are produced as acidic (hydrochloric acid) salts, which increases their solubility and stability of solutions. In tissues the salts dissociate to form the pharmacologically active cation. The salts dissociate in tissues to form the

pharmacologically active cation and hydrolysis produces a free base, so that in the body's environment the local anaesthetics exist as a non-ionised base and as a cation. Ionised forms bind more actively to receptors located on the inner surface of the nerve cell membrane, whereas non-ionised forms penetrate the cell membrane much more easily.

The ratio of these forms depends on the dissociation constant of the local anaesthetic, the pH of the solution and the pH value at the injection site. In an acidic environment, such as in inflammation, dissociation is delayed. This explains the significant decrease of drug activity in inflamed tissues.

*Classification*. According to their chemical structure, local anaesthetics are divided into two groups with different pharmacokinetic characteristics: the para-aminobenzoic acid ester (PABA) group and the amide group (Table 17.1). They are divided into 4 groups according to their clinical use:

1. For terminal (superficial) anaesthesia: cocaine, benzocaine, tetracaine, lidocaine, trimecaine, pyromecaine;

2. For conduction anaesthesia: procaine, lidocaine and trimekaine;

3. For infiltration anaesthesia: procaine, lidocaine and trimekaine;

4. For spinal anaesthesia: mepivacaine, bupivacaine, procaine, lidocaine.

**Table 17.1 Classification of local anaesthetics by chemical structure**

| PABA esters | Amides |
|---|---|
| Cocaine* | Lidocaine (xylocaine) |
| Procaine (novocaine) | Trimecaine (trimecaine) |
| Tetracaine (dicaine) | Mepivacaine (mepivastetzine) |
| Benzocaine (anesthesia) | Bupivacaine (marcaine) |
| | Articaine (ultracaine) |

* First ever local anaesthetic. Due to its high toxicity, it is hardly ever used today.

*Mechanism of action.* Topical anaesthetics produce a reversible loss of tissue sensitivity (firstly pain, then taste, temperature and tactile sensation) in a limited area of the body. By penetrating the lipoprotein layer, they block the plasma membrane of the nerve fibre or receptor, reducing its permeability to the ions that generate excitation and conduct nerve impulses. They increase the excitation threshold and lengthen the

refractory period, reduce the rate of onset and amplitude of action potentials and disrupt impulse conduction along the nerve.

As local anaesthetics are more active on open or inactivated channels, they primarily affect sensitive (pain) nerve fibres, which have a higher frequency and duration of depolarisation.

An increase in extracellular calcium partially blocks the effect of local anaesthetics, while an increase in extracellular potassium enhances their effect by stimulating inactivation of sodium channels.

**Main therapeutic effects.**

*Effects on sensory and motor functions.* Pain sensitivity is suppressed first, due to the more pronounced effect of local anaesthetics on thin nerve fibres, which have a higher impulse frequency and a comparatively longer action potential. With increasing concentration, other types of sensation are blocked and then motor functions are blocked. Myelinated fibers from the tactile receptors are resistant to local anesthetics, which explains why tactile sensitivity and pressure sensation is maintained during surgery despite adequate anesthesia. In conduction anaesthesia the sequence of function blocks is reversed: motor blockade occurs earlier than sensory blockade, because in large nerves the motor fibres are located in the periphery and first come into contact with the injected drug in the surrounding tissues.

*Relaxation of smooth and striated muscles* with high doses of local anaesthetics develops due to a decrease in intracellular calcium concentration. Recovery of contractility occurs within 30 days.

*Mild neuromuscular block* caused by local anaesthetics, is of no clinical significance. Almost all local anaesthetics (already in therapeutic doses) have a small vasodilatory effect. This effect weakens local anaesthesia. The exception is cocaine, which has a vasospastic effect. The antibacterial activity of tetracaine, procaine and lidocaine, proven in vitro, is of clinical importance only when taking material for bacteriological examination, where false negative results are possible.

*Effect on the respiratory system.* Local anaesthetics do not inhibit respiration, but potentiate the depressant effect of narcotic analgesics and anaesthetic agents. Local anaesthetics on the respiratory mucosa inhibit the laryngeal and cough reflexes, allowing aspiration of pharyngeal contents. This relaxes bronchial smooth muscles and increases bronchial secretion.

*Antiarrhythmic action* develops as a result of blockade of "fast" sodium channels of cardiac conduction system. Impulse generation and conduction in myocardial cells

proceed in the same way as in nerves, so local anaesthetics have a similar effect on cardiomyocytes. Some of them, e.g. lidocaine in concentrations lower than those required for anaesthesia, have antiarrhythmic effects, but all of them in high concentrations achievable in anaesthesia can provoke arrhythmias.

**Pharmacokinetics.**

*Absorption.* The degree of absorption of local anaesthetics from the OM is dependent on the type of drug and its concentration. Well absorbed agents (benzocaine, tetracaine, lidocaine) are used for superficial anaesthesia. Applied to the OM or wound surface, they are rapidly absorbed and reach plasma concentrations that are close to those of injectable anaesthesia. Application to areas with abundant blood flow results in very rapid absorption and higher blood levels than injection into areas with less active blood flow. After injection, the maximum concentration of local anaesthetics in the blood is usually reached after 10-25 minutes. An increased rate of absorption is also seen from the inflammatory zone, leading to systemic reactions. Therefore, local anaesthetics are not recommended to be administered in the area of inflammation.

There is a correlation between the efficacy of a local anaesthetic and its structure: the smaller the molecule, the faster it interacts with the sodium channels. The effect is also directly related to the ability of the local anaesthetics to dissolve in fat, while retaining sufficient hydrophilicity to allow diffusion to the site of action.

The more lipophilic bupivacaine, tetracaine have a stronger and longer action than procaine, lidocaine.

Among factors influencing post-injection absorption, the most clinically relevant are:

- physico-chemical properties of the drug substance;
- the binding of the drug to the tissues;
- dose of medication; -place of administration
- place of administration;
- state of circulation in the area of injection;
- the presence of inflammation in the area of injection;
- the use of a vasoconstrictor.

Vasoconstrictors such as epinephrine (adrenaline), norepinephrine (noradrenaline) and vasopressin are used to reduce absorption of local anaesthetics, reducing blood flow in the injection area. This is particularly significant for medium- and short-acting drugs (procaine, lidocaine). Reducing local blood flow and absorption

increases the concentration and thus the effect of the local anaesthetic in the treatment area and reduces the overall unwanted effects by reducing its concentration in the blood. The combination of decreased local absorption and increased nerve uptake of the local anaesthetic results in a 50% prolongation of its action. From Table. 17.2, could be seen the effect of a vasoconstrictor on the duration of action of anesthetics. When using long-acting fat-soluble local anesthetics (bupivacaine), the effect of a vasoconstrictor is much less pronounced, possibly because the molecules of these drugs have strong bonds with tissues.

**Table 17.2: Effect of the vasoconstrictor on the duration of action of some local anaesthetics**

| Drugs | Anaesthesia duration (min) | |
|---|---|---|
| | without vasoconstrictor | with vasoconstrictor |
| Procaine | 15-30 | 30-40 |
| Lidocaine | 30-60 | 120-130 |
| Mepivacaine | 45-90 | 120-360 |
| Articaine | 60 | 180 |
| Bupivacaine | 120-240 | 180-240 |

Different concentrations of epinephrine are used in dentistry, from 1/25000 to 1/300000; the most commonly used dilutions are 1/50000-1/80000-1/100000. The total dose of epinephrine should not exceed 0.2-0.25 mg (and norepinephrine 0.25-0.34 mg). In co-morbidities that increase the likelihood of complications, a minimum epinephrine concentration of 1/200000 is recommended.

When a vasoconstrictor is used, may develop such adverse effects:

- ~ decrease in potassium concentrations:
- ~ decrease in plasma potassium concentration, which in patients with initial hypokalemia receiving loop diuretics may have arrhythmogenic effects;
- ~ anxiety, tremor, cold extremities, tachycardia, arterial hypertension, headache;
- ~ at high doses or intravascular injection - cardiac arrhythmias, pulmonary oedema, seizures, cerebral haemorrhages; danger of ischaemia and ischaemic necroses.

The use of vasoconstrictors is contraindicated in:

- ~ decompensated cardiovascular disease;
- ~ had myocardial infarction within the last 6 months;
- ~ severe arterial hypertension;
- ~ diabetes mellitus;
- ~ hyperthyroidism;
- ~ a history of seizure syndrome;
- ~ therapy with antidepressants, GCS, beta-adrenoceptor blockers.

*Binding to plasma proteins* in amide drugs is 55-95%. For example, bupivacaine binds up to 95% and has a long-lasting effect, while procaine binds only 6% and has a short-lasting effect. Increased plasma protein levels in cancer patients, surgery, trauma, myocardial infarction, smoking, uremia reduces the risk of adverse effects of local anaesthetics. Hypoproteinemia, e.g. in liver disease, in neonates increases the risk of systemic adverse effects.

*Distribution*. As local anaesthetics from the ester group have a short half-life, their distribution in body tissues is poorly understood.

The amides are distributed in the body in two phases:

1. fast distribution phase with accumulation in well perfused tissues (brain, heart, kidney, liver);
2. slow distribution phase with uptake into muscle, adipose tissue.

Bupivacaine binds firmly to cell membrane structures, providing a strong and prolonged anaesthetic effect, but with increased risk of cardiotoxicity and arrhythmias.

*Metabolism and elimination.* The esters are hydrolysed in the blood by pseudocholinesterase and have a short elimination half-life (procaine, less than one minute).

The amides are hydrolysed by microsomal liver enzymes. Therefore, in patients with impaired liver function (liver disease, slowed hepatic blood flow) their biotransformation is delayed. For example, the half-life of lidocaine in liver damage increases from 1.8 hours to 6 hours or more.

By converting in the body to more hydrophilic metabolites than the parent substances, local anaesthetics are excreted in the urine.

**Undesirable effects.**

A. *Systemic.*

*Systemic undesirable effects*, with the exception of allergic reactions, are a consequence of high plasma concentrations in absolute or relative overdose, particularly when administered intravascularly. The use of local anaesthetics at the recommended doses (see below) is relatively safe. The greatest risk of adverse effects is during the first 30 minutes after injection when maximum plasma concentrations are reached.

In *the nervous system*, drowsiness, dizziness may occur, visual and hearing impairment, motor restlessness, nystagmus, muscle tremors, tonic-clonic convulsions, CNS depression to the point of coma, respiratory arrest and death.

Hypercapnia and acidosis increase the risk of seizures. If large doses are necessary, benzodiazepines, such as diazepam 0.1-0.2 mg/kg parenterally, can prevent convulsions. Convulsions, local anaesthetics can be treated with short-dose short-acting barbiturates, such as thiopental 1-2 mg/kg or diazepam - 0.1 mg/kg intravenously. In particularly severe cases, patients are ventilated with short-acting muscle relaxants.

*Psychogenic reactions* that occur when an anesthetic is injected, may be manifested by increased excitability of the patient or the development of faint.

The adverse effects of local anaesthetics on *the heart* are due to both direct effects on cardiomyocyte membranes and effects on autonomic nerve fibres; cardiac rhythm and conduction abnormalities, decreased myocardial contractility and hypotension. Bupivacaine has the greatest cardiotoxicity. Risk factors include hypoxemia, hypercapnia, acidosis, anemia, hypoproteinemia, hypovolemia, kidney disease, liver disease.

*Blood system*. Methemoglobinemia, manifested by cyanosis and a chocolate colour of the blood, respiratory disorders and dizziness, is possible in increased absorption of benzocaine in children and in overdose. Treatment consists of administration of methylene blue or ascorbic acid.

*Allergic reactions* are more often caused by preparations of the ester group, as their metabolism produces para-aminobenzoic acid derivatives (PABA), which is associated with the development of hypersensitivity. Cross-allergy has been observed between different esters as well as other PABA derivatives. Amides cause allergic reactions less frequently, but in a significant number of people, particularly with bronchial asthma, an allergy to bisulphite added to a vasoconstrictor topical anaesthetic

in carpules has been observed. In allergic patients, carpules and ampoules containing methylparaben, a stabilizer similar in chemical structure to PABA, should not be used in allergic patients.

B. *Local effects*.

*Peripheral neurotoxicity*. Large doses of local anaesthetics when applied have a toxic effect on the nerve.

Local complications resulting from *trauma associated with the insertion and slow administration of anaesthetic* may prevent needle penetration through the tissue at the injection site or by injecting the local anaesthetic solution into the injection site:

- ~ the contents of a single carpoule (1.8 or 2.2 ml) are injected within 1 minute;
- ~ local anaesthetic solutions with a vasoconstrictor have a more acidic pH (approximately 3.5) than the pure vasoconstrictor solutions and a few drops of the pure vasoconstrictor solution will increase patient comfort;

*Paresthesias* are usually associated with the procedure itself and are very rarely caused by local anaesthetics, more so with concentrated solutions.

*Infectious complications* can be minimised by the use of disposable needles and syringes, carpulated preparations; they can be associated with the introduction of local anaesthetic into an infected area and the "pushing" of infected material under pressure into a previously uninfected area;

*Ischaemia, necrosis and soft tissue damage* sometimes develop after administration of a local anaesthetic with a vasoconstrictor to the palatal tissue (severe and prolonged tissue ischaemia leading to development of necrosis and a sterile abscess);

*Soft tissue injury* associated with the patient biting the tongue or lip,

Injury to the soft tissue associated with the patient biting the tongue or lip may occur with long-acting medication and is more common in children and mentally disturbed patients; choose an agent that has an appropriate duration of action for the treatment, and warn parents or carers of the potential for self-harm and the need to avoid eating, hot drinks and biting the lips and tongue until the numbness has subsided.

The individual local anaesthetics differ both in their anaesthetic activity and in the severity and frequency of adverse effects. A comparison of these characteristics can

be made by taking the anaesthetic activity and toxicity of procaine as one unit (Table 17.3).

**Table 17.3: Comparison of anaesthetic activity and toxicity of local anaesthetics**

| Drug | Activity | |
|---|---|---|
| | Anaesthetic | Toxic |
| Procaine | 1 | 1 |
| Trimecaine | 3 | 1,5 |
| Lidocaine | 4 | 2 |
| Mepivacaine | 4 | 2 |
| Articaine | 5 | 1,5 |
| Bupivacaine | 6 | 7 |

The plasma concentration determines not only the frequency of adverse effects but also their nature.

**Drug interactions.**

The use of local anesthetics in patients receiving beta-adrenoblockers (anapriline, sotalol), antiarrhythmic agents (amiodarone), MAO inhibitors, tricyclic antidepressants, antipsychotics increase the risk of adverse effects. The risk of arrhythmias increases with the combined use of bupivacaine (and possibly other local anaesthetics) with halothane.

Topical anaesthetic solutions containing vasoconstrictors should not be used in patients receiving beta-adrenoblockers, neuroleptics droperidol, haloperidol, chlorpomazine and other phenothiazines.

Clinically relevant drug interactions of selected local anaesthetics are shown in Table 17.4.

**Table 17.4: Clinically relevant drug interactions of local anaesthetics**

| Anaesthetic | Drug | Effect |
|---|---|---|
| Procaine | Anaesthetic agents, sleeping pills, sedatives, | When administered intravascularly increases |

| | | |
|---|---|---|
| | narcotic analgesics and tranquillizers | the depressant effect on CNS |
| | Sulphonamides | Reduced antimicrobial activity |
| Tetracaine | Contact with alkalis (on instruments and syringes) | Forms an insoluble base |
| | Sulphonamides | Reduction of antimicrobial activity |
| Benzocaine | Non-narcotic analgesics and anticholinesterase agents | Increasing the activity |
| | Sulphonamides | Reduction of antimicrobial activity |
| Lidocaine | Cimetidine and propranolol | Decrease in hepatic clearance |
| | Barbiturates, phenytoin, rifampicin | Increase biotransformation into liver |
| | Aymalin, phenytoin, verapamil, quinidine, amiodarone | Increased negative inotropic effect |
| | Beta-adrenoblockers | Increased risk of bradycardia |
| | Digitoxin | Impairment of cardiotonic effect |
| | Novocainamide | CNS agitation, hallucinations |
| | Hexenal or sodium thiopental | Respiratory depression |
| | MAO inhibitors | Potential increase in local anesthetic effect |
| | Polymyxin B | Suppression of neuromuscular transmission |
| | Sleeping pills and sedatives | Increase in CNS depression |
| Trimekaine | Clinically relevant interactions apply only to vasoconstrictors (see above). | |
| Mepivacaine | Beta-adrenoblockers, antagonists of calcium, other antiarrhythmic agents | Increased depressant effect on conduction and contractility myocardium |

| | | |
|---|---|---|
| Bupivacaine | MAO inhibitors, tricyclic antidepressants | Arterial hypotension |
| | Oxytocin, ergotamine | Persistent arterial hypertension |
| | Halothane | Increased risk of arrhythmias |
| Articaine | Tricyclic antidepressants, MAO inhibitors | Increase the hypertensive effect |

**Clinical features of local anaesthetics.**

The universal contraindication for all local anaesthetics is individual intolerance to the drug or allergy to agents that cross-react with the given agent (which is of particular importance for PABA esters). Other contraindications are individual for each preparation.

Contraindications to the use of individual local anaesthetics are given in Table 17.5.

**Table 17.5 Contraindications to the use of selected local anaesthetics**

| Drugs | Contraindications |
|---|---|
| Procaine | Young age (under 14 years), emergency surgery accompanied by acute blood loss, marked fibrous changes in the tissue (for anaesthesia creeping infiltrate method). |
| Tetracaine | Young age (under 10 years), severe somatic diseases. With caution - decreased plasma cholinesterase activity, arrhythmias a-b blockade, shock, pregnancy, lactation. |
| Benzocaine | With caution - children (under 2 years), period of lactation. |
| Lidocaine | Methemoglobinemia, severe bleeding, infectious lesions in suspected place of anaesthesia, septicaemia, arterial hypotension, shock, ACSU, grade II-III a-blockade, marked bradycardia, arterial hypotension, cardiogenic shock, Stage II-III heart failure, intraventricular conduction disorders, renal impairment, severe myasthenia gravis, epileptiform seizures (including in anamnesis). Supraventricular arrhythmias. Pregnancy, lactation (for strict indications only), children (below 12 years of age). |
| Trimekaine | SSRIs, significant sinus bradycardia, a-v-blockade, cardiogenic |

| | |
|---|---|
| | shock. With caution - liver failure, renal failure, heart failure. |
| Mepivacaine | Severe liver disease, porphyria, severe myasthenia gravis. With caution - pregnancy, older age, severe cardiovascular disease, diabetes mellitus, vascular disease. |
| Bupivacaine | Thyrotoxicosis, heart failure, arterial hypotension, cardiogenic or hypovolemic shock, liver failure, young age (under 12 years of age). It is not used for intravenous regional anaesthesia. With caution - pregnancy, lactation. |
| Articaine | Megaloblastic B12-deficient anaemia, paroxysmal tachycardia, atrial tachyarrhythmia, closed-angle glaucoma, CNS disorders, chronic hypoxia, bronchial asthma. With caution - in women in labour with preeclampsia, haemorrhage in the third trimester of pregnancy. |

In addition to the characteristics of the local anesthetic itself (its efficacy, pharmacokinetic characteristics - absorption, excretion, adverse effects, etc.), the safety of anaesthesia is influenced by a number of patient-related factors. Before performing a masse), the safety of anaesthesia is influenced by a number of patient-related factors. Before local anaesthesia is carried out, a patient's anamnesis should be taken, and the presence of concomitant diseases, bad habits and underlying medication should be ascertained, he or she may be receiving. It is important to find out if local anaesthesia has been used before, and if there have been any complications. The dentist should know the patient's complete therapeutic diagnosis, including the stage of the disease, existing complications and their degree of compensation, symptoms of possible exacerbations, date of the patient's last visit to the attending physician (general practitioner, cardiologist, general practitioner etc.). Pulse rate, blood pressure and respiratory rate should be measured before anaesthesia is started. Information collected in this way may indicate the presence of risk factors.

*Factors affecting the safety of local anaesthesia:*

- Age (children, elderly patients).
- Weight (overweight).
- Physiological status (including pregnancy, lactation).
- Companion diseases (epilepsy, cardiac conduction disorders, bradycardia, congestive heart failure, angina pectoris, MI less than 6 months old, porphyria, anaemia, hepatic and renal impairment, chronic respiratory insufficiency, bronchial asthma, hyperthyroidism, diabetes mellitus).
- Clinical condition at the time of dental care.
- Basic drug therapy.

~ Allergy history, drug intolerance.
~ Vascularisation, inflammation in the affected area.

The safest way to prevent complications from anaesthesia is to dosing and avoiding overdosing is the safest way to prevent anaesthesia complications.

**Table 17.6 Maximum allowable doses of local anaesthetics**

| Anaesthetic | Dosage (mg/kg) | |
|---|---|---|
| | without vasoconstrictor | with vasoconstrictor |
| Procaine | 7 | 14 |
| Lidocaine | 4,5 | 7 |
| Mepivacaine | 4,5 | 6,5 |
| Bupivacaine | 1,3 | 2 |
| Articaine | 5 | 7 in adults (5 in children) |

If the amount of dental treatment requires the use of a local anaesthetic at a dose above 50% of the maximum allowable dose, it must be ensured that the patient can receive intensive care support, if necessary, including free access for intravenous injections, oxygen inhalation assisted or ventilated ventilation.

To prevent intravascular administration of the local anaesthetic, it is recommended that aspiration tests be carried out before and during each administration and that the volumes of solutions recommended for this type of dental intervention are not exceeded.

Eating is allowed only after recovery of sensitivity.

*Local anaesthesia in pregnancy*. The use of local anaesthetics in pregnant women, especially in large doses, can have adverse effects on the foetus. Articaine is the safest and can be used throughout pregnancy. Bupivacaine has the greatest cardiotoxicity in pregnant women and is therefore not used in them.

*Local anaesthesia in lactation*. Local anaesthetics pass into breast milk in small amounts. Articaine is considered the safest local anaesthetic in breastfeeding women. Trimecaine (trimecaine, trimecaine hydrochloride, trimecaine with norepinephrine).

It is similar to lidocaine, but has a lower diffusion capacity, which lengthens the latency period and increases drug consumption during conduction anaesthesia.

For surface anaesthesia a 2-5% solution of up to 200 mg is used. For infiltration anaesthesia a 0.125-0.5% solution is used in a dose of up to 2 g. For percutaneous anaesthesia a 1-2% solution is used in a dose of up to 800 mg without and up to 1200mg with an epinephrine supplement of 1:200000. It is available in 0.25%, 0.5%, 1%, 2% and 5% solution in 1, 2, 5 and 10 ml ampoules.

*Mepivacaine* (mepivastesin, mepidont). Has a fast and strong action. For all types of injection anaesthesia, 3% solution without vasoconstrictor or 2% solution with epinephrine (1:8000, 1:100000) or norepinephrine(1:200000).

It is available as a 3% solution for injection in 1.7 and 1.8 ml cartridges and as a 2% solution for epinephrine (1:100000) in 1.8 ml cartridges.

*Bupivacaine* (anecaine, marcaine). It is 4 times more active than lidocaine. Long action, long latency period and high cardiotoxicity. The action lasts after the anaesthesia is completed, which is used for relief of post-operative pain.

For infiltration anaesthesia 0.25% solution is used in doses up to 1.5 mg/kg.
For percutaneous anaesthesia a 0.25-0.35% solution is used in a dose of up to 2 mg/kg.

The addition of a vasoconstrictor slightly prolongs the effect of bupivacaine and does not limit absorption of the drug into the systemic bloodstream.

It is available as 0.25 and 0.5% solution for injection in 4 ml ampoules and 20 ml vials.

*Articaine* (articaine hydrochloride, alfacaine, brilocaine-adrenaline, septonest with epinephrine, ultracaine, ubistezine, cytocartin). Has a shorter latency period and longer duration of action than lidocaine. Good diffusivity and high anaesthetic activity allows low concentrations of vasoconstrictors and expands indications for its use in high-risk patients. Low lipophilicity and high plasma protein binding (95%),The use of the amino acids is associated with less tissue penetration from the vascular system and less severe systemic adverse effects. The cardiotoxic effects are less pronounced than those of other amide local anaesthetics. It is effective and of low toxicity in inflammation of the OM. It is used in children and elderly patients. It poorly penetrates through the placental barrier.

The placental barrier and is the drug of choice in pregnant women. Its low toxicity allows its use during lactation.

For infiltration anaesthesia use 1% with or without epinephrine (1:200000). For percutaneous anaesthesia a 1-2% solution is used in a dose of up to 400-600 mg.

In uncomplicated upper jaw teeth extraction in non-inflammatory stage - vestibular depot 1.7 ml per tooth, if necessary additional 1-1.7 ml; small incision or suture - palatal depot 0.1 ml.

When removing mandibular premolars in the uncomplicated stage, infiltration anaesthesia has the effect of guiding anaesthesia. For cavity preparations and preparation of teeth for crowns (except lower jaw molars) vestibular injection 0.5-1.7 ml per tooth.

It is available in a form of powder substance, 1%, 2% and 4% solution for injection in 5 and 20 ml ampoules, 1.7 and 1.8 ml glass cartridges and inserts without and with epinephrine 1:100000, 1:200000.

## Control questions

1. Which statement is correct?

a) the ionised form of local anaesthetics penetrates easily through cell membranes.
b) the ability of local anesthetics to block sodium channels depends on the structure of the channel.
c) the anesthetic effect is enhanced when vasoconstrictors are added by enhancing the effect on the CNS.
d) highly lipophilic local anaesthetics have a longer duration of action.
e) all are correct.

2.Choose a correct statement:

a) local anaesthetics reversibly block the conduction of the pain impulse.
b) the anaesthetic effect is independent of the dose of the drug.
c) local anaesthesia is not used in children.
d) bupivacaine is safest with respect to cardiac adverse effects.
e) all are correct.

3.Choose the correct statement:

a) the strength and duration of analgesia is proportional to the concentration of the local anaesthetic on the surface of the nerve fibre.
b) local anaesthetics have a weak but clinically significant local vasodilator effect.
c) increased extracellular potassium potentiates the analgesic effect of local anesthetics.
d) the smaller the local anesthetic molecule, the faster it interacts with sodium channels.
e) all are correct.

4. Which statement is wrong?

a) local anaesthetics of the PABA ester group often cause allergic reactions.
b) bupivacaine is contraindicated in pregnancy.
c) local anesthetic solutions with vasoconstrictors are contraindicated in patients with arrhythmias.
d) the efficacy of local anaesthetics is enhanced in an acidic environment. E. The toxic effects of local anesthetics are dose dependent.

5. The toxic effects of local anaesthetics include all but:

a) tonic-clonic seizures.
b) anaphylactic reactions.
c) visual disturbances.
d) arrhythmias.
e) CNS depression.

6. Which statement is true for local anaesthetics from the amide group?

a) they are stable in solutions.
b) they are slowly metabolized in the liver.
c) they relatively rarely cause allergic reactions.
d) the risk of overdose of these drugs is increased in patients with liver disease.
e) all are correct.

7. Select the correct statement regarding procaine:

a) has a quick and short duration of action.
b) hepatotoxic.
c) rarely causes allergic reactions.
d) the drug of choice in pregnant women.
e) all are correct.

8. Local anaesthetic solutions containing vasoconstrictors are not recommended for use in patients:

a) with rheumatoid polyarthritis.
b) with thyrotoxicosis.
c) with baseline GCS therapy.
d) with bronchial asthma.
e) those receiving NSAIDs.

9. When performing local anaesthesia in children:

a) bupivacaine is used to provide prolonged anaesthesia.
b) maximum concentrations of vasoconstrictors are used to reduce systemic adverse effects.
c) applicative anaesthesia is used to anaesthetise the injection site. D. thick short needles are used to administer the anaesthetic
d) administering local anaesthesia in children is not indicated.

10. Which undesirable effect cannot be caused by vasoconstrictors?

a) tachycardia.
b) arrhythmias.
c) hypokalemia.
d) bronchospasm.
e) increased BP.

# Chapter 18. Sedatives and benzodiazepine receptor antagonists.

*Psychotropic (psychopharmacological) drugs* are medical treatments that have a predominantly psychiatric effect. These medications work through neurotransmitter systems that transmit nerve impulses from one neuron terminal to another via the synaptic cleft. Such mediators include noradrenaline, dopamine (D), serotonin (5-NT), acetylcholine, GABA, histamine, opioid peptides (endorphins, dynorphins, enkephalins), prostaglandins. In addition, psychotropic drugs alter biochemical and electrical processes in the CNS, affecting biochemical processes related to enzymes, receptors, ionic tubules, neurotransmitter and messenger systems. They are involved in mechanisms of release, active reuptake, bind to various subtypes of pre- and postsynaptic receptors or their constituents.

The localisation of neurons functioning with the neurotransmitters studied suggests the presence of entities in which the points of application of drugs used in mental illnesses are located:

- ~ the cerebral cortex,
- ~ reticular formation (attention, arousal, anxiety),
- ~ limbic system (affective or emotional content),
- ~ hypothalamus (autonomic nervous system regulation, pituitary-endocrine control).

The classification of psychotropic drugs is shown in Figure 19.1, depending on their effect on the CNS, drugs can be divided into:

- ~ Psycholeptics - having a sedative (deprivative) effect (neuroleptics, tranquilizers, sedatives).
- ~ Psychoanaleptics - which have an energising, stimulating effect (antidepressants, psychostimulants, adaptogens).
- ~ Non-antimotics - medicines that have a preventive effect during phasic and intermittent psychosis(lithium salts).
- ~ Psychosleptics - drugs causing short-term psychotic states (ketamine is used in psychiatry and drug psychotherapy, used for scientific purposes to simulate mental states).

This chapter will mainly focus on sedatives and tranquillisers.

*Tranquillisers* (lat. Tranquillo - to make you calm, serene) are medicines that reduce feelings of anxiety, fear and emotional tension, while minimally suppressing the CNS. As their main effect is to suppress anxiety, they are also called *anxiolytics*. Drugs in this group are widely used in medicine to treat anxiety, insomnia, panic attacks, seizures, skeletal muscle spasms and as an anaesthetic and analgesic component. Tranquillisers that can induce sleep by shortening the period of onset and/or prolonging its duration, are used as *hypnotics* (sleeping pills). Drugs that do not induce significant drowsiness and muscle relaxation are called *daytime tranquillisers.*

**Indications for use in dentistry:**

- ~ To reduce psycho-emotional tension and fear before a visit to the dentist;
- ~ As a pre-medication before local or general anaesthesia;
- ~ As a component of general anaesthesia;
- ~ For relief of facial muscle spasm associated with malocclusion and temporomandibular joint involvement;
- ~ For emergency treatment of seizure syndrome.

*Classification.* There are several classifications of anxiolytics depending on the nature of their action, chemical structure, etc.

Depending on their chemical structure, anxiolytics are divided into benzodiazepine derivatives, the most numerous, effective and frequently used group, and derivatives of other chemical structures (Table 18.1). They can also be divided into tranquillisers proper (diazepam, etc.), hypnotics (nitrazepam, flunitrazepam, midazolam, zolpidem, etc.), sedatives (combined drugs with barbiturates, phyto-drugs, etc.) A distinction is made between long-acting (e.g. diazepam, phenazepam, nitrazepam), medium-acting (chlordiazepoxide, lorazepam, nosepam, alprazolam etc.) and short-acting (midazolam, triazolam) drugs.

According to D.A. Harkiewicz classification, according to mechanism of action anxiolytics can be divided into the following groups:

- ~ benzodiazepine receptor agonists (diazepam, phenazepam etc.);
- ~ serotonin receptor agonists (buspirone);
- ~ serotonin receptor agonists (buspirone);
- ~ miscellaneous agents (benactisine, etc.).

**Table 18.1: Classification of tranquillizers according to structure.**

| | |
|---|---|
| Benzodiazepines | Diazepam, chlordiazepoxide, nitrazepam, phenazepam, oxazepam, lorazepam, flunitrazepam |
| Triazolobenzodiazepines | Alprazolam, triazolam, madisopam |
| Heterocyclic | Brotizopam |
| Diphenylmethane derivatives | Benactisine, hydroxyzine |
| Heterocyclic derivatives (propanediol) | Busperone, zopiclone, clomethysol, hemineurin, zolpidem |
| Various structures | Gamma amino-beta-phenyl butyric acid hydrochloride (phenibut). |

**Mechanism of action.**

The main tranquilliser benzodiazepines bind to specific receptors (benzodiazepine receptors) located on the membranes of neurons and increase the sensitivity of the GABA receptor to its mediator. This enhances the inhibitory effect of GABA on the transmission of nerve impulses in all parts of the CNS. Depending on the dose, benzodiazepines have CNS depressant effects of varying severity: from mild sedative to hypnotic, and in overdose, to coma.

Tranquillisers from other chemical groups are also able to bind to GABA receptors in the limbic system. Phenibut acts on GABA receptors in the CNS, facilitates GABAergic transmission of impulses and improves bioenergetic processes in the brain. Some drugs affect central histamine receptors of H1-type. Diphenylmethane derivatives actively affect cholinergic systems of the brain, and therefore they are also called central cholinolytics. Propanediol derivatives do not have a pronounced effect on benzodiazepine and cholinergic receptors.

Some drugs have an inhibitory effect on polysynaptic reflexes and transmission via insertion neurons and in high doses may inhibit conduction along the neuromuscular synapse, resulting in a myorelaxant effect. Main therapeutic effects. Traditionally, tranquillisers are distinguished by 6 main effects, the severity of each of which and their ratio vary widely from one drug to another.

*The sedative effect* is to inhibit reactions to persistent stimuli with a decrease in spontaneous activity and thinking.

*Anxiolytic* or *tranquilising (sedative) effects* are manifested by a reduction of anxiety, fear, emotional tension.

*The myorelaxant* (central myorelaxant) effect can be seen as a positive clinical effect when using anxiolytics to relieve tension, fear, agitation, as well as muscle spasms and general anaesthesia, but often the resulting feeling of weakness, lethargy and fatigue limits the use of tranquillisers.

All benzodiazepines, but especially those with a short T1/2, have a hypnotic or hypnotic effect by reducing the duration of falling asleep, the number of awakenings and increasing the total duration of sleep, depending on the dose used.

The autonomic stabilising effect is to regulate the activity of the autonomic nervous system; it is used to relieve neurovegetative manifestations of anxiety and diencephalic crises.

The anticonvulsant effect is seen in doses that do not cause deep suppression of CNS function, i.e. when mental and physical activity is maintained, and develops through direct suppression of CNS seizure activity.

There are at least 2 other important therapeutic effects used in analgesia:

1. Potentiation of the effects of narcotic and non-narcotic analgesics.
2. An antegrade amnesic effect, i.e. weakening of short-term (working) memory and impaired recall of events that occurred during achieved when benzodiazepines are administered parenterally as premedication.

Some anxiolytics have additional effects:

~ psychostimulant and thymoanaleptic;
~ antiphobic.

**Pharmacokinetics.**

*Absorption*. When taken orally, benzodiazepines are well absorbed from the gastrointestinal tract and reach maximal blood concentrations after 1-4 hours. Diazepam is absorbed more rapidly than other benzodiazepines and is used when an anxiolytic effect is required. Diazepam has low bioavailability when administered intramuscularly, whereas lorazepam is rapidly and completely absorbed. Absorption is influenced by the lipophilicity and acidity of the drugs.

*Binding to plasma proteins*. Benzodiazepines have a 60-95% (up to 99% for diazepam) binds to plasma proteins. Patients who are hypoproteinemic are more sensitive to them. Distribution in the body. The rapidity and duration of action of benzodiazepines depends on their fat solubility. The more lipophilic ones penetrate into the CNS more rapidly but also redistribute from it into adipose tissue more rapidly. Redistribution of benzodiazepines leads to cessation of their main clinical effects. Thus, the more lipophilic diazepam acts more quickly than the less lipophilic chlordiazepoxide and lorazepam, but the effects of the latter are longer lasting. Benzodiazepines penetrate the placental barrier well.

*Metabolism and elimination*. All benzodiazepines are metabolised in the liver to form active and inactive metabolites. Most drugs are oxidised by hepatic microsomal enzymes, the resulting metabolites are finally inactivated and excreted as glucuronides in the urine and partially (10%) in the faeces. Some benzodiazepines (lorazepam) are metabolised by binding to glucuronic acid without prior oxidation.

The active metabolites formed during biotransformation of long-acting benzodiazepines have an even longer elimination half-life than the main drug, which delays elimination and may lead to cumulation (Table 18.2).

With age or liver disease, the elimination half-life of benzodiazepines may be more than doubled, which also contributes to cumulation. In these cases, oxazepam and lorazepam, which are metabolised by direct binding to glucuronic acid, are preferable to oxidative metabolism, which is less dependent on age or baseline liver status.

**Table 18.2: Excretion of some benzodiazepines and their active metabolites**.

| Drugs | $T_{1/2}$ (hour) | Active metabolites and their T (hour) |
|---|---|---|
| Diazepam | 3 (53 if repeatedly administered) | N-desmethyldiazepam, 50-99<br>Oxazepam, 5-12 |
| Lorazepam | 10-20 | - |
| Chlordiazepoxide | 9-18 | Desmethylchlorodiazepoxide, 10-1<br>Demoxepam, 35-50 |
| Oxazepam | 5-12 | - |
| Medazepam | 1-2 | Diazepam |
| Midazolam | 2 | 7-α-hydroxytriazolam, 4-6 |

**Undesirable effects.**

*Sedation* is the most persistent complication of the use of anxiolytics, and in particular benzodiazepines. Increased fatigue, general weakness, drowsiness, depression, impaired concentration, difficulty remembering new information, forgetfulness - particularly pronounced with long-acting drugs, which is dangerous for transport drivers and other professions that require concentration and quick reactions.

*The cardiodepressant effect* of benzodiazepines is dose-dependent and is primarily seen in hypovolemia and heart failure, when normal doses may cause arterial hypotension due to vasomotor depression. Toxic doses inhibit myocardial contractility and vascular tone through not only central but also peripheral effects and may cause hypotension, bradycardia, cardiac arrest.

Even small doses of benzodiazepines can cause *respiratory depression* in patients with obstructive lung disease, both by reducing respiratory centre sensitivity to carbon dioxide and by central myorelaxant action. In overdose of tranquillisers, the main cause of death is respiratory depression.

Respiratory and cardiovascular adverse effects develop more frequently with intravenous administration.

*Tolerance* occurs with prolonged use. Reduced response to the drug due to decreased reactivity of the nervous system (pharmacodynamic tolerance) requires a progressive increase in dose to obtain the same effect. A partial cross-tolerance may develop between tranquillisers, sleeping pills and alcohol.

*Local irritant effects* develop with parenteral administration (more common with diazepam).

*Mental and physical dependence*, up to and including true substance abuse, is manifested by the development of withdrawal symptoms following abrupt cessation of the drug (insomnia, anxiety, loss of appetite, tremors and sweating, etc.). Dependence develops after a few weeks of regular therapeutic doses, although it can form more quickly. It is generally assumed that short-acting preparations are faster and more severe. However, it may take from 3-4 days to 2-3 weeks before clinical withdrawal symptoms appear (some symptoms may be present within a few hours of withdrawal of short-acting drugs and some symptoms may be present for several months after the long-acting drugs). Therefore, the following rules should be observed when prescribing benzodiazepine tranquillisers:

- Start with the lowest possible dose.
- Do not prescribe benzodiazepines to young patients.
- Do not prescribe benzodiazepines to young people.
- If you do not notice an improvement within 4-6 weeks, then discontinue treatment.

~ Preferably use antidepressants for panic attacks, phobic disorder. Beta-blockers should be used for autonomic symptoms.
~ Prescribe for a limited period of time.
~ Prefer treatment of anxiety with benzodiazepines with a long half-life.
~ Elderly and somatically debilitated patients should be prescribed drugs without active metabolites.
~ Care should be taken with patients who are susceptible to addiction.
~ Continuous monitoring of patients receiving benzodiazepines.

Rare adverse effects:

~ Paradoxical reaction in the form of motor agitation, irritability, aggressiveness, increased anxiety;
~ Euphoria may occur with regular use of benzodiazepines, headaches, dizziness, perceptual problems (including auditory comprehension) and hallucinations (more often when taking alcohol or other drugs), drug use, taking other CNS-depressant drugs), paresthesias, gastrointestinal dysfunctions, liver disorders, decreased libido, the appearance of muscle weakness, muscle spasm, laryngospasm, ataxia, urinary incontinence, cytopenia, hypersensitivity reactions, weight changes.

See Table 18.3 for drug and other interactions.

**Table 18.3 Drug and other interactions.**

| Drug interactions | Benzodiazepine drugs | Result interactions |
|---|---|---|
| Alcohol, anaesthetics, opioid analgesics, antidepressants, neuroleptics, alpha-adrenoblockers, antihistamines | All | Increasing of sedative effect |
| Erythromycin | Oxidising in the liver agents (diazepam) or recoverable | Inhibition of biotransformation and increasing of benzodiazepines concentrations in the blood |
| Isoniazid | Diazepam | Inhibition of biotransformation and |

| | | |
|---|---|---|
| | | increase of diazepam concentrations in the blood |
| Rifampicin | Diazepam, possibly others | Increasing of diazepam biotransformation |
| Ketonezole, fluconazole, diltiazem, verapamil | Midazolam | Increasing of midazolam concentrations in the blood |
| Hypotensive | All | Increasing the hypotensive effect |
| Cimetidine | Oxidising in the liver | Inhibition of biotransformation and increasing of benzodiazepines concentrations in the blood |
| Omeprazole | Diazepam | Inhibition of biotransformation and increasing of diazepam concentrations in the blood |

**Contraindications to the use of benzodiazepines are:**

- ~ An allergic reaction to one of the medicines in this group
- ~ Shock, coma
- ~ Severe hepatic or renal impairment
- ~ Myasthenia gravis
- ~ Porphyria
- ~ Closed-angle glaucoma (including suspected)
- ~ Acute alcohol intoxication, intoxication with narcotic analgesics,
- ~ sleeping pills
- ~ Ataxia (impaired coordination of movements)
- ~ Serious cardiac or respiratory failure
- ~ Pregnancy
- ~ Lactation
- ~ Infancy (up to 5 weeks)
- ~ Nighttime apnoea syndrome (more frequent and longer periods of apnoea)

Local anaesthesia in children. Before administering local anaesthesia to a child the dentist should take a thorough history and obtain parental consent for the planned treatment. It is important to explain to the child in language that is understandable for their age, what the dentist will do and why it is necessary. Benzodiazepines should be used with particular caution in patients in risk groups at risk:

- ~ Elderly and old age (use short-acting drugs and reduce doses by half; parenteral use carries a high risk of apnoea, hypotension, bradycardia and cardiac arrest).
- ~ Children (children, especially young children, are very sensitive to CNS depressant effects).
- ~ Abstructive lung disease.
- ~ Abuse of alcohol.
- ~ A history of psychotropic drug abuse or addiction (predisposition to addiction and dependence).
- ~ Moderate hepatic or renal impairment (dose reduction, selection of a drug whose elimination is not associated with impaired function).
- ~ Hypoproteinemia (dose reduction required).
- ~ Organic brain disease (increased CNS depression).
- ~ Use of drugs that interact with benzodiazepines, especially drugs that cause CNS depression.

All tranquillisers are contraindicated in persons working with "dangerous" cars, driving and other activities which require increased attention.

*Use in pregnancy*. Benzodiazepines are contraindicated in pregnancy.

Its use in the first trimester increases the risk of congenital malformations; if used late in pregnancy, neonatal hyperthermia, hypotension, respiratory depression may develop; withdrawal symptoms in the infant may occur with regular use.

*Use during lactation*. Benzodiazepines penetrate into breast milk and their use in lactation is contraindicated.

*Use in children*. Children in the first week of life are not able to metabolise benzodiazepines.

**The drugs** .

*Diazepam* (diazepam, Relenium, Relium, seduxen, sibasone). Administered orally at 5-10 mg for 30-60 minutes before and during medication. 10 mg by mouth 30-60 minutes before an intervention; when given as a course of treatment, 2-5-10 mg three times a day, with an average daily dose of 15-30 mg. In patients over 60 years of age, the starting dose is 2 mg twice daily. By IV for short-term anaesthetic sleep in difficult diagnostic and therapeutic interventions, 20-30 mg is administered slowly (at a rate of 2.5 mg in 30 seconds). In children: 200-300 mcg/kg body weight or 1 mg per year of life. In case of a seizure, IV 10-20 mg, If necessary, 20 mg repeatedly after 30-60 min.

Available in 2, 5 and 10 mg tablets and 0.5% solution for injection in 2 ml ampoules (5 mg/ml).

*Lorazepam* (lorafen, apo-lorazepam). It is used for premedication in a dose of 2 mg orally one hour before surgery; when used as a course of treatment, 1 mg 2-3 times a day is given orally. In elderly and debilitated patients, the daily dose should not exceed 1-2 mg. Preferred in patients with non-serious liver dysfunction.

It is available in 1 and 2.5 mg drags; 0.5, 1, 2 mg tablets.

*Midazolam* (dormicum). It is used as an oral premedication in a dose of 15 mg (7.5 mg for elderly and debilitated patients) 30-40 min before the procedure; intravenously - 1-15 mg as an analgesic component; in children - 0.15-0.2 mg/kg of body weight, IV 2.5-5 mg 5-10 min before surgery; as a component of general analgesia.

It is available in 7.5 and 15 mg coated tablets and 0.5% solution for injection in 1 and 3 ml ampoules (5 mg/ml).

*Medazepam* (mesapam, rudotel). Used as a daytime tranquiliser.

Its myorelaxative and sedative effects are much less pronounced than those of the other benzodiazepines. It is administered orally in case of anxiety in dose of 10-20 mg 30-40 min before dental treatment and in case of sleep disturbance; the dose is decreased in 2 times in elderly people and in patients with kidney dysfunction.

It is available in 10-mg tablets.

*Oxazepam* (nosepam, tazepam). Inferior to diazepam in its tranquilising effects. It is used orally for anxiety, 5-10 mg 30-40 min before dental treatment. When used as an outpatient course of treatment, the average daily dose is 30-50 mg. Caution should be exercised if the patient is prone to hypotension.

It is available in 10 mg tablets.

*Bromodihydrochlorophenylbenzodiazepine* (phenazepam). It has a more pronounced anxiolytic effect than most other benzodiazepines and has a sedative effect. It is given orally up to 0.5-1.0 mg 40-60 min before an intervention. For a course of treatment, 0.25-0.5 mg two to three times a day; the average daily dose is 2-3 mg. For premedication or for relief of fear, anxiety, psychomotor agitation, vegetative paroxysms, 0.5-1 mg is administered by injection or intravenously (by stream or drop). The dose is reduced by a factor of 2 in elderly people.

It is available in 0.5, 1 and 2.5 mg tablets and 0.1% solution for intravenous and intramuscular administration in 1 ml ampoules.

*Chlordiazepoxide* (chlorazepide, elenium). It is administered orally. For premedication a dose of 5-10 mg is administered 40-60 min before the intervention (two to four doses of 5-10 mg can be administered during the day before the intervention). When administered as a course the average daily dose is 30-50 mg in 3-4 doses.

It is available in coated tablets of 5 and 10 mg.

*Tofizopam* (Grandaxin) It is intermediate between minor tranquillisers and psychoenergetics. It has an effect on the limbic system, middle and lower reticular structures and other structures. It has anxiolytic effect, does not influence mental concentration and ability to work. It is used for diseases accompanied by vegetative disorders, tension, apathy, anxiety, fatigue, restlessness, reactive depression, pseudo-angina pains.

It is available in 0.05 g tablets. It is usually taken 1-2 tablets 1-3 times a day as a course of treatment.

*Flumazenil* (anexat) is a benzodiazepine derivative with high affinity for benzodiazepine receptors and no stimulant effect; acts as a competitive antagonist. Eliminates central effects of benzodiazepines but does not prevent effects of other sedatives, hypnotics, ethanol on CNS, opioids, general anaesthetics.

*Indication*: Benzodiazepine overdose.

*Pharmacokinetics*. Its effect is rapid but not prolonged during IV administration.

It is metabolised to form an inactive metabolite, which is excreted in the bile.

*The elimination half-life* is 50-60 min. The effects of benzodiazepines last longer than those of flumazenil, requiring repeated administration.

*Adverse effects*: hypersensitivity reactions, agitation, dizziness, nausea, impaired consciousness, seizures may develop in patients with a history of epilepsy; intracranial pressure may increase in patients with craniocerebral injuries; patients with physical dependence on benzodiazepines develop a severe withdrawal syndrome. Refrain from work requiring increased attention during the day.

Dosage mode: intravenously at 0.2 mg for 15 s (with possible subsequent administration of 0.1 mg every minute up to a maximum dose of 1 mg).

Available as 0.01% solution for intravenous administration in 5 ml ampoules.

## **Control questions**.

1. A dentist administered a premedication drug which made the patient feel drowsy for a day after injection. Patient has noticed daytime lethargy. Identify this drug.

a) ketorolol.
b) diazepam.
c) atropine.
d) fentanyl.
e) diclofenac.

2.When diazepam is used, all undesirable effects are possible except:

a) muscle weakness.
b) arterial hypotension during parenteral administration.
c) respiratory disturbance during parenteral administration.
d) dependence on prolonged administration.
e) Raynaud's syndrome.

3.In which patients is there an increased risk of adverse effects of benzodiazepines?

a) members of the Negro race.
b) alcoholics.
c) women.
d) peptic ulcer patients.
e) patients with benign prostatic hyperplasia.

4.Which of the following statements is not correct?

a) biotransformation of lorazepam does not produce active metabolites.
b) diazepam is used in patients with liver dysfunction.
c) bromodihydrochlorophenylbenzodiazepine has marked tranquilizing activity.
d) impaired concentration develops after use of benzodiazepines.
e) benzodiazepines are used in reduced doses in elderly patients.

5.Interaction of benzodiazepines with which drugs is there an increase in sedation?

a) antihistamines.
b) rifampicin.
c) hypotensive drugs.
d) diuretics.
e) all are correct.

6.Of the following statements, indicate the incorrect one.

a) Biotransformation of diazepam produces active metabolites that have a longer T1/2 than diazepam.
b) Physical and mental dependence develops with long-term use of benzodiazepines.
c) Benzodiazepines are used to manage hypertension.
d) Regular use of benzodiazepines is contraindicated in patients with nocturnal apnoea syndrome.
e) Flumazenil is used in benzodiazepine overdoses.

7.Which of the following may not contribute to the cumulation of benzodiazepines?

a) impaired liver function.
b) older and older age.
c) alcoholism.
d) smoking.
e) administration of erythromycin.

8.What effects are possible when diazepam is given intravenously?

a) respiratory depression.
b) hypotension.
c) anterograde amnesia.
d) bradycardia.
e) all are correct.

9.Which undesirable effect cannot develop when using benzodiazepines?

a) acute renal failure.
b) mental and physical dependence.
c) withdrawal syndrome.
d) xerostomia.
e) daytime sleepiness.

10.Which drug is indicated to relieve facial muscle spasm.

a) ketamine.
b) ketorolol.
c) diazepam.
d) thiopental.
e) lornoxicam.

# Chapter 19. Narcotic opioid analgesics and opioid receptor antagonists

*Opioids* are all natural and semi-synthetic derivatives of opium alkaloids (*opiates*), synthetic morphine-mimicking drugs and *opiopeptins* - endogenous substances such as, for example, enkephalins and endorphins.

**Indications for use in dentistry:**

- ~ Capitation of acute and chronic pain syndrome in dental diseases, including cancer;
- ~ As a premedication during preparation and carrying out of stomatological interventions.

**Classification.**

A class of narcotic analgesics includes morphine and other natural opiate alkaloids, as well as synthetic compounds with morphine-like properties. A single term, opioids, is now used to refer to all these substances.

Depending on the severity of the analgesic effect, a distinction is made between:

- ~ low-acting opioids for mild pain (codeine, pentazocine, tramadol);
- ~ high-acting opioids for use in severe pain (morphine, buprenorphine, fentanyl, trimepiridine).

**Mechanism of action.** Exogenous opioids, like endogenous opiopeptides, bind to specific opiate receptors. Different types of opiate receptors are identified in different parts of the nervous system and tissues of the human body: mu, kappa, delta, and sigma, each with its own spectrum of effects (Table 19.1) and have several subtypes. Analgesic effects, euphoria, respiratory depression, the ability to cause physical dependence are mainly due to interactions with mu- and delta-receptors. Kappa receptor activation leads to analgesia at the spinal level. In addition, a number of the effects of opioids are thought to (hallucinogenic, cardio-stimulant and some other), can be related to another receptor type, sigma receptors.

**Table 19.1: Effects of opiate receptor activation**

| Mu-receptors | Kappa- receptors | Delta-receptors | Sigma-receptors |
|---|---|---|---|
| Supraspinal analgesia. Respiratory depression. Euphoria. Physical dependence. Miosis. | Spinal analgesia, Respiratory depression, Sedation, Miosis | Supraspinal analgesia, Respiratory depression | Hallucinogenic effect, Delirium, Dysphoria, Respiratory depression. Cardiostimulant effect |

Activation of specific receptors leads to disruption of transmembrane potassium and calcium currents, inhibition of neurotransmitter release, inhibition of pain impulse transmission at spinal level, increase of pain threshold, which is accompanied by development of analgesia. In some opioids (tramadol), the clinical effects are mediated through the ability to inhibit the neuronal reuptake of serotonin and noradrenaline from the synaptic cleft in addition to the receptor action. Opioids include receptor-activating compounds – agonists (morphine, trimepiridine), receptor-blocking antagonists (naloxone) and substances which act as either receptor agonists or antagonists, depending on the dose - antagonist agonists or partial agonists (butorphanol, pentazocine). The dose-dependence of the action of antagonist agonists determines their narrow therapeutic range.

In the drug dependent patient, they, acting as antagonists, may cause withdrawal syndrome. Agonists with a weak analgesic effect (codeine) may compete for the receptor with highly active opioids (morphine) and thereby weaken the effects of the latter. With increasing doses, selectivity is lost and the pharmacological properties of the drug may change. Some drugs, especially antagonist agonists, act at several receptors in common doses and may stimulate some and block others.

**Main therapeutic effects**. In addition to analgesia, many additional pharmacological effects are possible with opioids, some of which, depending on the situation and their severity, may be regarded as therapeutic or as undesirable actions.

*CNS:*

- ~ sedative effect, helping to reduce the emotional component of pain and to control the autonomic and motor manifestations of pain;
- ~ respiratory depression, which helps to reduce respiratory muscle work and cardiac output in the case of pulmonary oedema, while a decrease in BP helps to reduce foaming;
- ~ cough reflex suppression to treat a dry, debilitating cough.

*Cardiovascular system:*

- ~ peripheral vasodilation, involving both the arterial and, to a greater extent, the venous system, which provides a reduction in venous return to the heart, reducing preload; used in the management of angina status and pulmonary oedema;
- ~ reducing myocardial oxygen consumption, reduce myocardial oxygen consumption, which plays a primary role in controlling angina attacks.

*GIT*:

- ~ suppression of peristalsis, which is used in non-infectious diarrhoea.

In addition, opioids cause the following pharmacodynamic effects that need to be taken into account, including in the diagnosis of overdose and abuse:

- ~ Myiasis;
- ~ Torso muscle stiffness;
- ~ Nausea and vomiting;
- ~ Inhibition of renal function;
- ~ Longer labour by decreasing uterine tone.

**Pharmacokinetics.**

*Bioavailability*. Most opioids are well absorbed from subcutaneous and intramuscular sites as well as the mucosa of the mouth, nose and gastro-intestinal tract. Fentanyl penetrates the skin well and can therefore be used transdermally. However, despite rapid absorption, the bioavailability of many drugs, e.g. codeine, when taken orally is low due to a pronounced first-pass effect through the liver, where they are metabolised to form glucuronides. And the amount of enzyme involved in this reaction may vary from person to person, so the effective dose is sometimes difficult to predict.

*Binding to plasma proteins*. A smaller proportion of the administered dose (on average 20-35%) is bound to plasma proteins.

*Distribution*. Opioids are rapidly distributed in the body and accumulate in tissues with a high perfusion coefficient (lungs, liver, kidneys, spleen). In skeletal muscle their concentrations are lower, however, due to their large mass they are the main reservoir of these substances. Lipophilic drugs accumulate in adipose tissue, especially when administered frequently. Codeine and heroin penetrate the blood-brain barrier better than others; morphine penetrates poorly. Opioids penetrate the placenta

and breast milk well, and may cause respiratory depression and drug dependence in the foetus and neonate.

*Metabolism and elimination*. Most opioids are metabolised in the body, in particular, they are conjugated to glucuronic acid. They are formed as active(e.g. up to 10% of a dose of codeine is converted to morphine) and inactive metabolites are produced. Metabolites and the remainder of the unchanged substance are excreted in the urine. In patients with impaired renal function, accumulation of the active substances may occur, with the development of deeper analgesia and undesirable effects. In patients with significant hepatic impairment, administration of opioids is undesirable, which are metabolised to glucuronides in the liver are undesirable.

**Undesired effects**

*Restlessness, dysphoria with a feeling of discomfort* and lassitude develop in some patients and in healthy individuals who are not in pain.

*Drowsiness, blurred consciousness*, impaired ability to think logically are common undesirable effects associated with the prescription of narcotic analgesics. Sleep induced by therapeutic doses of opioids is usually superficial and easily interrupted. It is more often seen in young people than in the elderly.

*Respiratory depression*, the extent of which depends on the specific opioid and its dose. A variety of stimuli, including pain, may stimulate breathing. Cessation of pain by an opioid may significantly increase respiratory depression. Persons with increased intracranial pressure, bronchial asthma and other lung diseases have a worse tolerance. Suppression of the respiratory centre combined with *suppression of the cough reflex*, which may be accompanied by impaired sputum production, may lead to increased respiratory depression.

Opioid analgesics cause *nausea and vomiting* due to activation of the brainstem trigger chemoreceptor zone. When moving, these symptoms are exacerbated by the effects on the vestibular apparatus.

The action of opioids on the *gastrointestinal tract* is mediated through both the CNS and opioid receptors, which have a high density directly in the walls of the stomach, small and large intestine and sphincters. When administered, even in therapeutic doses may lead to increased tone and spasm of the smooth muscles, particularly the sphincters, suppression of peristalsis, constipation, colic, decreased gastric secretion. Spasm of the Oddi sphincter leads to impaired pancreatic juice outflow, development of biliary and pancreatic reflux, and elevated blood levels of lipase and amylase.

Opioids used in clinical practice have no discernible effect on *cardiovascular system.* Bradycardia associated with vagotonia may be observed. BP usually remains unchanged, except in patients with hypovolemia, who may develop orthostatic hypotension as a result of peripheral vasodilation. Increased intracranial pressure as a result of increased cerebral blood flow, developing due to dilatation of cerebral vessels in response to carbon dioxide accumulation during respiratory depression. In other cases there is no change in cerebral blood flow.

*Tolerance, physical and mental dependence*

When morphine and its analogues are used frequently, a reduction in analgesic effects occurs, i.e. tolerance develops, requiring an increase in the dose of the medication. Physical dependence develops in parallel with tolerance: an opioid becomes necessary. Withdrawal leads to a withdrawal syndrome, which manifests itself in a specific clinical picture with severe subjective sensations and life-threatening objective changes. The development of tolerance and dependence represents a true cellular adaptive response and does not depend on the pharmacokinetic parameters of the drugs. Severe physical dependence develops within 10-20 days of taking opium. Tolerance is cross-tolerant, i.e. once developed to one opioid, it affects any other.

The peculiar pleasure experienced by addicts leads to increased consumption of the opioid and the formation of psychic dependence, which is even stronger with the development of physical dependence, when only regular consumption of the drug provides a "normal", "comfortable" way of life. Mental dependence develops within 3-4 months with opium, 2 months with morphine and considerably more rapidly with heroin.

The most obvious diagnostic sign of opioid use is abrupt constriction of the pupils when taking opioids ("pin-head") as well as pale skin, shortness of breath and decrease in body temperature. Emaciation, jaundice and haemorrhage are characteristic of drug users and injection marks may be observed on the skin.

**Drug interactions**.

Agonist-antagonist-drug interactions with opioid receptor agonists reduce the analgesic effect of the agonists and may lead to withdrawal symptoms in drug users.

Alcohol, sedatives, neuroleptics increase the CNS depression of opioids, including respiratory depression; hypotension may increase.

There is a possibility of seizure syndrome in combination use of tramadol and tricyclic antidepressants. The analgesic effect of tramadol is reduced in patients receiving carbamazepine.

Concomitant use of opioids with MAO inhibitors may lead to hyperthermic coma; BP may increase.

Decreased plasma concentrations of ciprofloxacin have been reported with opioids.

Prokinetics (metoclopramide and domperidone) reduce the gastrointestinal effects of opioids.

**Contraindications to the use of opioids:**

- ~ Acute or severe chronic respiratory depression.
- ~ Acute alcohol intoxication.
- ~ Paralytic ileus.
- ~ Acute abdominal syndrome or suspected; abdominal pain of unclear genesis.
- ~ Intracranial hypertension, craniocerebral trauma or suspected.
- ~ Pheochromocytoma.
- ~ Severe hepatic insufficiency.
- ~ Age less than 2.5 years.

Use with extreme caution, adjusting doses, and only for strict indications in patients in the risk group, which include:

- ~ Elderly and old age.
- ~ Severe cachexia.
- ~ Arterial hypotension.
- ~ Decreased thyroid and adrenal cortex function.
- ~ Bronchial asthma and other variants of COPD (only in remission, in the absence of symptoms of respiratory failure).
- ~ Benign prostatic hyperplasia.
- ~ Kidney and liver disorders (dose adjustment required).
- ~ Pancreatitis, condition after cholecystectomy, intestinal diverticulosis.
- ~ Convulsive syndrome in the anamnesis.
- ~ Substance abuse.
- ~ Pregnancy and lactation (opioids are class C drugs).

*Use in pregnancy*

Continued use of opioids in pregnant women may lead to the development of physical dependence in the foetus as manifested by withdrawal symptoms in the early postnatal period.

*Lactation use*

Opioids pass into breast milk and should not be used in breastfeeding patients.

**The drugs**

*Morphine* is a strong opioid receptor agonist and is the mainstay of treatment of severe pain. It is used for premedication, post-operative pain relief. In emergency cardiology, it is used for treatment of angina syndrome, acute left ventricular failure.
Its onset of action is observed after 10-15 minutes after injection and after 20-30 minutes when administered orally, its duration of action is 3-5 hours. The usual single analgesic dose of morphine when administered by injection and ingestion is 10mg. The maximum daily dose for adults is 50 mg, but in cancer patients with chronic pain syndrome it can be as much as 1 g.

It is available (morphine, morphine hydrochloride) in the form of a 1% solution for injections of 1 ml (ampoules, syringes, tubes). In the treatment of chronic pain, it is available orally in tablets, depot tablets and slow-release tablets.

*Trimeperidine* (promedol) is a synthetic opiate receptor agonist, it is inferior to morphine in its analgesic activity. Fentanyl is a potent short-acting synthetic opiate receptor agonist with an analgesic effect 100 times greater than morphine. It penetrates the blood-brain barrier well; it induces analgesia 2 min after IV administration. The duration of action after a single injection does not exceed 30 min. It is used exclusively for analgesia during surgical operations.

It is available as 0.005% solution for injection in 1, 2 ml (ampoules). The transdermal patch form is used to treat severe pain, mainly in cancer patients.

*Codeine* is an opiate receptor agonist with low analgesic activity, used for the treatment of mild acute and chronic pain, often in combination with an NSAID (paracetamol, acetylsalicylic acid, ibuprofen). In high doses it causes agitation. A dependence on codeine develops, but is considerably less pronounced than with morphine. It is used as a symptomatic agent in dry coughs. Analgesic effects occur 30-60 minutes after oral administration and last for 4-6 hours. It is used orally at 10-60 mg, every 3-6 hours. The highest daily dose is 120 mg.

It is available as a substance; the offical forms are registered in the Russian Federation only as combination drugs.

*Butorphanol* (moradol, stadol) is an agonist-antagonist of opiate receptors. Compared with morphine, it has greater analgesic activity, less respiratory depression and less narcogenic potential. The duration of action is 3-4 hours. It does not affect sphincter tone or gastrointestinal motility. In the early postoperative period after fentanyl-based anaesthesia it can reduce residual effects of fentanyl, including depression of respiration, having its own analgesic effect. It is used in mild to severe pain syndrome, for premedication and for general anaesthesia. It should not be used in conjunction with opioid receptor agonists due to because of its antagonistic activity.

It is administered in 1-2 mg i.v., 2-4 mg i.m., with repeated injections after 3-6 hours. In elderly patients with impaired hepatic and/or renal function, the dose is reduced by half and the interval between doses is 6 hours.

It is available as 0.2% solution for injection in 1 and 2 ml (ampoules).

*Tramadol* (tramadol, mabron, tramadol) is a synthetic opioid with a mixed mechanism of action. It is used to treat moderate pain. In therapeutic doses, it is much less likely to cause harmful adverse effects, that are characteristic of morphine. The likelihood of developing tolerance and resistance is very low, even after many months of use; withdrawal is mild in comparison with other opioid analgesics. The most common adverse effects are dry mouth, drowsiness and nausea. However, their intensity is low and usually does not require withdrawal. When taken orally, the analgesic effect develops in 20-30 min and lasts for 4-6 hours. The first dose for pain syndrome is 50-100 mg. The daily dose should not exceed 400 mg, and for patients over 75 years of age, 300 mg. Dosage adjustment is required in patients with CKD and liver disease.

Available in 50 mg capsules; in drops (vials) and solution-drops for oral administration (vials, vials with dispenser and vials with dropper) 100 mg in 1 ml of 10 and 96ml; in slow-release tablets (retard) of 100, 150 and 200 mg (with duration of action up to 10-12 hours); in rectal suppositories of 100 mg and as 5% solution for injection (ampoules) of 1 and 2 ml.

*Pentazocine* (Fortral) is an opioid receptor agonist-antagonist with inferior analgesic activity to but superior to butorphanol in its frequency of adverse effects and narcogenic potential.For analgesia, it is administered in 30-60 mg v/v, v/m, p/k at intervals of 2-4 hours, orally - 50 mg 3-4 times a day; maximum daily dose if used orally is 350 mg.

Available as 50 mg tablets and 1 ml 3% solution for injection (ampoules).

**Opioid receptor antagonist**

*Naloxone* (naloxone, narcan) is a universal opiate receptor antagonist, which displaces opioids from binding to all receptor subtypes. It is used for opioid overdose, opioid-induced respiratory depression and in situations where the cause of respiratory depression is unknown.

With intravenous administration, action begins after 2 minutes; with p/u and i/m, it takes less than 5 minutes; maximum effect is achieved after 5-15 minutes; its duration depends on the dose and route of administration and may be 45 minutes (with intravenous administration considerably less). Respiratory distress may reoccur after discontinuation as the duration of action of the opioid may be longer than that of naloxone.

*Use with caution* in addicts (provocation of withdrawal). Safety in pregnant women and children has not been established.

*Adverse effects*: arterial hypotension or hypertension, ventricular tachycardia may occur with rapid administration and high doses, ventricular fibrillation, pulmonary edema, seizure, tremor, sweating, nausea, vomiting; allergic reactions possible.

*Contraindications*: Hypersensitivity to the drug.

In life-threatening conditions, it is administered by IV in a dose of 0.4-0.8 mg, up to 2.0 mg.

To prolong the effect, part of the dose may be administered in m/m or p/u. If there is no effect, the dose may be repeated after 2-3 minutes. If there is no response after a total dose of 10 mg and 10 minutes after naloxone has been administered, the diagnosis should be reviewed.

An IV dose of 0.01 mg/kg is used in children.

In postoperative narcotic respiratory depression, naloxone is given by IV 0.1-0.2 mg every 2-3 min in an attempt to restore breathing while maintaining partial analgesia.

It is available as a 0.4-mg/ml solution for injection (ampoules).

## Control questions

1.Tramadol differs from morphine in that:

a) extremely rarely causes respiratory depression at the therapeutic dose.
b) causes greater physical and mental dependence.
c) often causes bradycardia.
d) is more effective in controlling severe pain.
e) all of the above are true.

2.What are some of the undesirable effects of morphine?

a) urinary retention.
b) constipation.
c) physical dependence.
d) acute hepatic encephalopathy.
e) muscle weakness.

3.What are the indications for the use of naloxone?

a) respiratory depression in overdose of barbiturates.
b) management of severe pain.
c) opioid-induced respiratory depression.
d) pain control in acute myocardial infarction in the addict.
e) premedication.

4.What is characteristic for codeine?

a) used to relieve mild to moderate pain.
b) has an anti-coughing effect.
c) significantly less addictive than morphine.
d) in high doses, causes agitation.
e) all of the above are true.

5.Which of the following statements is incorrect?

a) The combination of codeine and paracetamol has a more pronounced analgesic effect than the mono-component drugs.
b) Naloxone is used for opioid-induced respiratory disorders.
c) Parenteral administration of analgesics is used in the management of acute pain syndrome.
d) Promedol is used to relieve postoperative pain after tooth extraction.
e) The prescription of narcotic analgesics in cancer patients is not limited to the development of physical craving.

6.What is characteristic of opiate receptor agonist-antagonists?

a) may cause withdrawal symptoms in a morphine dependent patient.
b) are more physically demanding than morphine.
c) can cause respiratory depression when used in therapeutic doses.
d) have no narcogenic potential.
e) used for pain management of low intensity.

7.Which is true of fentanyl?

a) a synthetic opioid with pronounced analgesic effects.
b) has a short duration of action when administered parenterally.
c) can be used transdermally.
d) promptly causes physical dependence.
e) all of the above are correct.

8.Which conditions require opioid dose reduction?

a) IBS.
b) arterial hypertension.
c) chronic liver disease.
d) osteoarthritis.
e) hyperthyroidism.

9.Which statement is true?

a) Narcotic analgesics are contraindicated in elderly patients.
b) Morphine causes an increase in pulmonary artery pressure.
c) Tramadol does not cause urinary disorders.
d) Naloxone is used for premedication.
e) The combination of acetylsalicylic acid and codeine is used to relieve severe pain syndrome.

10.Which statement is incorrect about butorphanol?

a) an opiate receptor agonist-antagonist.
b) used as a component of premedication and general anaesthesia.
c) as an opioid receptor antagonist has a weaker effect than naloxone.
d) less likely to be physically dependant than morphine.
e) used in conjunction with fentanyl and other opioid receptor agonists.

# Chapter 20. Pain, analgesia, analgesics.

*Pain* is an unpleasant sensory and emotional condition caused by actual or potential tissue damage.

The definition of "pain" covers:

- ~ a painful stimulus that communicates actual or impending tissue damage,
- ~ a personal, individual perception of a harmful factor,
- ~ a set of responses designed to protect the body from the disease-causing factor,
- ~ a category of experience based on multiple events, accompanied by sensory and emotional states.

**The classification** of pain syndromes according to aetiology (IASP):

1. *Nociceptive*.
   - ~ Somatic (affection of soft tissues, bones, skin, muscles)
   - ~ Visceral (abdominal effusion, organ capsule overstretching).

Nociceptive pain is initially defensive but with prolonged irritation (more than 3 months) it becomes an aggravating factor of the underlying disease and leads to chronic pain syndrome.

2.*Neuropathic*. It occurs during the stages of nerve impulse transmission from the pain receptor (nociceptors) to the neurons of the spinal cord and higher CNS.

3.*Psychogenic*. Originates in response to individually significant psychological influences.

Pain is divided into acute and chronic depending on its duration.

Treatment tactics differ.

The most common forms of pain are:

- ~ Headache;
- ~ Pain related to musculoskeletal system disorders;
- ~ Tooth pain;
- ~ Dysmenorrhoea.

Fig. 20.1: Stepwise treatment of chronic pain syndrome.

When treating chronic pain, analgesics should be given in preference to oral analgesics:

- ~ prefer oral administration of analgesics;
- ~ use effective doses; the route of administration should ensure a stable analgesic effect;
- ~ administer analgesics regularly rather than during the onset of severe pain;
- ~ use effective analgesics; the route of administration should ensure a stable analgesic effect.

In terminal cancer patients, the main aim of treatment is to relieve pain, and the development of tolerance and dependence is not essential.

In both acute and chronic pain syndromes, combination analgesics are widely used, the efficacy and safety of which are presented in Table 20.3.

**Table 20.3 Efficacy and safety of combinations of analgesic drugs.**

| Combination | Analgesic effect | Safety | Note |
|---|---|---|---|
| NSAID + gastrointestinal mucous membrane protector (synthetic prostaglandin) | Does not increase | Increases | Indicated in group of patients with risk of development of gastropathy |
| Paracetamol/acetylsalicylic acid + mild opioid (codeine) | Increases | Increased risk of development undesirable opioid effects | More rational is the usage of individual drugs |
| Ibuprofen + weak opioid (codeine) | Above or the same | ---“----------“--- | ---“----------“--- |
| NSAID + barbiturate (phenobarbital) | Does not increase | Increased risk of development of undesirable barbiturate effects | Combination is not rational |
| NSAIDs + caffeine | Does not increase | Caffeine stimulating effect | Combination is not rational |
| NSAIDs + vitamins | Does not increase | ? | Combination is not rational |

| | | | |
|---|---|---|---|
| Paracetamol/acetylsalicylic acid + methamisole sodium/ aminophenazone/butylphenazone | Higher (?) | Increased risk of undesirable effects | Combination should not be applied |

**Drugs**

*Acetaminophen* (paracetamol, Calpol, Panadol) - Tablets of 0.12 g; 0.125 g; 0.25 g; 0.25 g; 0.3 g; 0.5 g. Suspension and syrup 120 mg/5 ml. Oral solution 120 and 125 mg/5 ml. Adults: oral 0.5-1.0 g 4-6 times per day. Children: oral 10-15 mg/kg 4-6 times daily.

The level of analgesic and antipyretic effect is almost equivalent to aspirin. In contrast, paracetamol has minimal and clinically insignificant anti-inflammatory effects. This is due to the fact that paracetamol inhibits more prostaglandin synthesis in the CNS than in peripheral tissues.

It is well absorbed when taken orally and rectally. Maximum concentration in blood develops 0.5-2 hours after administration. Metabolized in the liver in 2 stages: firstly, intermediate metabolites are formed under the action of cytochrome P-450 enzyme systems, which are then broken down with the participation of glutathione. The elimination half-life is 2-2.5 hours.

*Paracetamol* is considered one of the safest NSAIDs. Unlike aspirin, it does not cause Ray's syndrome, and has no gastro-toxicity and no effect on platelet aggregation. Unlike the pyrazolones and pyrazolidines, it does not cause agranulocytosis and aplastic anaemia. Allergic reactions are rare. However, the development of analgesic nephropathy and renal failure is possible with prolonged systemic administration. A single dose of more than 10 g of paracetamol in adults or more than 140mg/kg in children leads to severe liver damage. This is due to depletion of glutathione stores and accumulation of paracetamol metabolic intermediates, that are hepatotoxic. Symptoms of poisoning appear on the 2nd or 3rd day: nausea, vomiting, clotting disorders, increased transaminase activity, sometimes jaundice.

Fatal outcome is possible. Measures of treatment: gastric lavage with activated charcoal, acetylcysteine (glutathione donor) - oral 20% solution, glucose intravenously, with an increase in the international normalised ratio (INR) of more than 2.5 preparations of vitamin K1 (phytomenadione - intramuscularly 1-10 mg), native plasma, clotting factors. Forced diuresis, peritoneal dialysis and haemodialysis are ineffective in

paracetamol poisoning. Antihistamines, glucocorticoids and phenobarbital, which enhance the formation of hepatotoxic metabolites, should not be used.

In dentistry, paracetamol may be considered as an alternative to aspirin for post-operative toothache, e.g. in patients with bleeding tendency, with bronchial asthma and in children. It is widely used for other pain syndromes and as an antipyretic. A dose-dependent analgesic effect has been observed: 1000 mg is generally more effective than 650 mg.

*Metamizole sodium* (Analgin, Dipyrone) - 0.1 g and 0.5 g tablets, 1 and 2 ml ampoules of 1 ml, ampoules, 1 ml and 2 ml of a 50% solution. Adults: orally 0.5-1.0 g 3-4 times/day, or v/m or iv 2-5 ml 50% solution 2-4 times/day. Children: 5-10 mg/kg 3-4 times/day.

It has a pronounced analgesic effect, which is caused mainly by central mechanisms, particularly by disruption of conduction of pain impulses in the spinal cord. It has no anti-inflammatory effect. It is rapidly and almost completely absorbed in the gastrointestinal tract. The maximum concentration in develops in the blood after 1-2 hours, the elimination half-life is 2.5 hours.

In dentistry it may be used for treatment of toothache. When in the case of fast-acting dentistry, it can be administered parenterally. As methamizole is a pyrazole derivative, its use there is a potential risk of aplastic anaemia or agranulocytosis.

Therefore, metamizole should not be administered to patients with haematopoietic disorders and should not be used in combination with other haematotoxic medicines.

## Control questions

1.Select a drug for moderate post-operative toothache in an adult patient with no risk factors:

a) indomethacin
b) celecoxib
c) promedol
d) ibuprofen
e) reopirin

2. Choose a medication for moderate post-operative toothache in an adult patient with haemorrhagic diathesis:

a) ketorolac
b) aspirin
c) paracetamol
d) phenylbutazone
e) citramon P

3.Choose the preparation for high intensity post-operative toothache in an adult patient with no risk factors:

a) aspirin
b) paracetamol
c) ketorolac
d) cedalgin-neo
e) pyroxicam

4. What are the most common adverse effects of sodium metamizole?

a) acute gastrointestinal erosions.
b) bronchoobstruction.
c) hemorrhagic syndrome.
d) leukopenia.
e) exacerbation of chronic colitis.

5. Which NSAID is indicated for the management of mild pain after
in a middle-aged patient with no risk factors?

a) celecoxib.
b) piroxicam.
c) ketorolac.
d) tramadol.
e) ibuprofen.

6. Which statement is incorrect about paracetamol?

a) It is contraindicated in liver dysfunction.
b) Can be used in children with viral infections.
c) Does not affect platelet aggregation
d) Allergic reactions may occur when taken.
e) Has pronounced analgesic, antipyretic and anti-inflammatory effects

# Chapter 21. Non-steroidal anti-inflammatory drugs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a group of medicines that prevent or reduce the intensity of an inflammatory response. In addition to their anti-inflammatory effects, NSAIDs also have analgesic and antipyretic effects. NSAIDs are among the most commonly used medicines; many of them are over-the-counter drugs.

**Indications for use in dentistry**:

~ treatment of inflammatory diseases of the maxillofacial region, periodontal disease, oral mucosa;
~ treatment of acute and chronic pain;
~ premedication before dental treatment.

Considering that NSAIDs are one of the most frequently used medicines, the dentist, as a general practitioner, also needs to be aware of other indications for their use.

*Chemical properties*. NSAIDs are mostly weak organic acids in their chemical structure. Some of them, such as nabumetone, are the precursors of the active drug with acidic properties (prodrugs).

*Classification.* There are several classifications of NSAIDs. Depending on the severity of the anti-inflammatory activity and the chemical structure, NSAIDs are subdivided as follows:

1. NSAIDs with pronounced anti-inflammatory activity
    - Acids
        - ◊ Salicylates
            - o Acetylsalicylic acid (aspirin)
            - o Diflunisal
            - o Lysinmonoacetylsalicylate
        - ◊ Pyrazolidines
            - o Phenylbutazone
        - ◊ Indoleacetic acid derivatives
            - o Indomethacin
            - o Sulindac
            - o Etodolac
        - ◊ Phenylacetic acid derivatives
            - o Diclofenac

- ◊ Oxycams
    - Pyroxicam
    - Tenoxicam
    - Lornoxicam
    - Meloxicam
    - Sudoxicam
- ◊ Propionic acid derivatives
    - Ibuprufen
    - Naproxen
    - Flurbiprofen
    - Ketoprofen
    - Thiaprofen acid

- Non-acidic derivatives
    - ◊ Alcanones
        - Nabumetone
    - ◊ Sulfonamide derivatives
        - Nimesulide
    - ◊ Coxibs
        - Celecoxib
        - Rofecoxib
        - Valdocoxib
        - Lumiracoxib
        - Parecoxib
        - Etoricoxib

2. NSAIDs with poor anti-inflammatory activity
    - Anthranilic acid derivatives
        - ◊ Mephenamic acid
        - ◊ Etophenamate
    - Pyrazolones
        - ◊ Metamizole
        - ◊ Aminophenazone
        - ◊ Propiphenazone
    - Paraaminophenol derivatives
        - ◊ Phenacetin
        - ◊ Paracetamol
    - Heteroarylacetic acid derivatives
        - ◊ Cetorolac .
3. Combined products
    - Arthrotec (diclofenac + misoprostol)

Another classification is based on the selectivity of NSAIDs in relation to their effect on the cyclooxygenase enzyme forms (Table 21.1).

**Table 21.1: Classification of NSAIDs according to selectivity towards different forms of COX.**

| | |
|---|---|
| Highly selective towards COX-1 | Acetylsalicylic acid (aspirin)<br>Indomethacin<br>Ketoprofen<br>Piroxicam |
| Moderate selectivity towards COX-1 | Diclofenac<br>Ibuprofen<br>Naproxen<br>Lornoxicam<br>Meloxicam |
| Selectivity towards COX-2 | Nimesulide<br>Celecoxib<br>Rofecoxib |

**Mechanism of action.**

All NSAIDs have identical points of action (Brook PM, 1993), among which are:

- ~ prostaglandin synthesis;
- ~ synthesis of leukotrienes;
- ~ formation of superoxide radicals;
- ~ release of lysosomal enzymes;
- ~ activation of cell membranes;
- ~ aggregation and adhesion of neutrophils;
- ~ function of lymphocytes;
- ~ synthesis of rheumatoid factor;
- ~ synthesis of cytokines;
- ~ cartilage metabolism.

Of the many mechanisms of NSAIDs, cyclooxygenase (COX) inhibition, a key inflammatory enzyme, plays a major role. COX inhibition disrupts the synthesis of prostaglandins (PGs) from arachidonic acid. PGs mediate the inflammatory response, cause exudation and oedema, sensitise receptors to pain mediators (histamine, bradykinin) and lower the threshold of pain sensitivity. They increase the sensitivity of

hypothalamic thermoregulatory centres to the action of pyrogens produced in the body by infectious agents, toxins.

There are at least two isoenzymes that regulate the synthesis of two different GH subclasses (Figure 21.1). COX-1 is constantly present in tissues and is involved in the synthesis of GHs that regulate the physiological functions of cells: platelets, gastrointestinal mucosal epithelium, vascular endothelium, etc. At the same time, the amount of COX-2 in the tissues is extremely low, and it increases sharply only in the course of the inflammatory reaction, which serves as one of the main pathogenetic mechanisms of inflammation. The suppression of COX-1 synthesis by the use of NSAIDs explains the nature of the main adverse effects of these drugs. The ratio of the severity of COX-1 and COX-2 inhibition allows NSAIDs to be ranked according to their safety level. Of the commonly used drugs, the least safe are piroxicam and indomethacin, while the safer ones are - acetylsalicylic acid, diclofenac, ketoprofen, ibuprofen. Several COX-2 selective inhibitors (celecoxib, meloxicam) have been synthesised in recent years, which have good analgesic and anti-inflammatory activity.

Figure 21.1: Current cyclo-oxygenase concept.

The likelihood of developing adverse effects increases in proportion to the dose of the drug (dose-dependent effect). For example, ibuprofen at a daily dose of up to 1200 mg is relatively safe but when the dose is increased to 2400-4800 mg, the incidence of adverse effects is comparable to that of other non-selective NSAIDs. In addition to the blockade of GH synthesis, other mechanisms of action of NSAIDs are also known (see above), the severity of which varies with individual agents. Sodium metamizole has been found to have the ability to inhibit the conduction of pain impulses in the spinal cord. It was found that anionic properties of NSAIDs allow them to penetrate into the bilayer of phospholipid membranes of immunocompetent cells and directly influence protein interaction, preventing cellular activation at early stages of inflammation. Some NSAIDs increase intracellular calcium levels in T-lymphocytes, which contributes to increased proliferation and synthesis of IL-2.

**Main therapeutic effects.**

Among the many effects of NSAIDs, anti-inflammatory, analgesic, antipyretic and antiaggregant are of most therapeutic importance.

*Anti-inflammatory effects*. NSAIDs can be ranked in the following order by severity of anti-inflammatory activity: indomethacin > diclofenac > pyroxicam > ketoprofen > naproxen >ibuprofen > aspirin, which is valid for medium therapeutic doses. The new COX-2 selective inhibitors (meloxicam and celecoxib) are as effective as diclofenac, piroxicam or naproxen. All NSAIDs inhibit the exudation phase. Some of

them, e.g. indomethacin, diclofenac, affect proliferation processes by reducing collagen synthesis. Although average therapeutic doses exist (Table 21.1)

There are significant differences in the effectiveness of NSAIDs in individual patients and in various inflammatory diseases, which dictates the need for individual selection of NSAIDs for each individual patient.

*Analgesic effect*. NSAIDs suppress mild to moderate levels of pain of somatic (soft tissue, bone, muscle spasm) and neuropathic (with damage to nerve structures) origin. In visceral pain associated with hollow and parenchymatous organ overstretching or carcinomatosis, they are less effective than opioids. At the same time, NSAIDs have fairly high analgesic activity for colic and postoperative pain.

Ketorolac, ibuprofen, ketoprofen, paracetamol, lornoxicam are widely used in dentistry for acute postoperative pain. The advantage of NSAIDs over opioids is that they do not depress the respiratory centre, do not cause euphoria, are not addictive and do not have an antispasmodic effect.

One reasonably safe agent for mild pain is paracetamol, which, unlike other drugs in this group, is central and does not block GH synthesis in the periphery and therefore has no anti-inflammatory and ulcerogenic effects as well as a significant effect on the blood coagulation system.

Ibuprofen is widely used for the management of moderate pain, one of the safest non-selective NSAIDs, which also has a moderate anti-inflammatory effect. When used in analgesic doses (up to 1200mg/day), it has a greater analgesic effect than paracetamol or aspirin at doses up to 3.0 g/day and is less likely to cause adverse effects.

Celecoxib in doses of 100-400 mg for dental surgery has analgesic effects similar to those of acetylsalicylic acid in doses of 500-1000mg.

In therapeutic doses (Table 21.2), all NSAIDs have similar analgesic effects to those of mild narcotic analgesics (codeine 60mg). The combination of paracetamol (600-650 mg) and codeine (60 mg) is more effective than each of these drugs alone.

*Antipyretic effect*. NSAIDs are effective in reducing fever and have no effect on normal body temperature. This effect is due to their effect on the thermoregulation centre in the hypothalamus, whereby the increased heat emission due to vasodilation of the skin surface vessels prevails over the inhibited heat production. The heat loss process is accompanied by significant sweating.

*Antiaggregant effect*. All NSAIDs reduce thromboxane production and inhibit platelet aggregation. Acetylsalicylic acid has the most clinically significant effect on platelet function. It irreversibly inhibits COX and blocks thromboxane synthesis in nonnuclear platelets, and therefore can not synthesize new enzymes for all their lifetime (from 5-8 to 11-14 days).

In practice, however, due to the different age of circulating platelets, the suppression of platelet aggregation persists for about 8 days. If the patient is to undergo surgery, acetylsalicylic acid should be discontinued one week before surgery.

The antiaggregant effect of other NSAIDs is weaker and reversible. Cases of increased bleeding due to the antiplatelet effect of ketorolac have been reported, which requires special caution when used in postoperative patients.

**Pharmacokinetics.**

*Absorption.* All NSAIDs are well absorbed in the gastrointestinal tract, their bioavailability is 75-90%, and the time to reach the maximum concentration in the blood is 2-3 hours. Ingestion of food and antacids reduces the bioavailability of most NSAIDs. The parenteral route of administration is used to provide emergency care for severe pain or when it is impossible to ingest, for example, with vomiting.

*Communication with plasma proteins*. Most NSAIDs are almost completely bound to plasma proteins (90-99%), while displacing other drugs from their association with plasma albumins. Dose reduction required in patients with hypoalbuminemia NSAIDs. The exceptions are acetylsalicylic acid and paracetamol, which bind to plasma proteins to a lesser extent.

*Distribution in the body*. NSAIDs are widely distributed throughout the body, reaching high concentrations in extracellular and synovial fluids. They pass through the placenta and in small amounts into breast milk.

The pharmacokinetics of NSAIDs is described by a two-chamber model, where one of the chambers is tissue and synovial fluid. The therapeutic effect of drugs in articular syndromes is to some extent associated with the rate of accumulation and the concentration of NSAIDs in the synovial fluid, which increases gradually and persists much longer than in the blood after discontinuation of the drug.

However, there is no direct correlation between their concentration in blood and synovial fluid.

*Metabolism and elimination*. All NSAIDs undergo biotransformation in the liver, therefore, in case of violation of its function, portal hypertension with the disclosure of porto-caval anastomoses may increase the concentration of drugs in the blood and the development of toxic reactions. Intoxications can also result from the accumulation of toxic metabolites. So, from paracetamol, in addition to inactive glucuronide and sulfate, a highly active N-acetylbenzoquinonimine is formed in a small amount, which is neutralized by conjugation with the thiol group of glutathione. When the reserves of the latter are depleted, the unbound toxic metabolite causes the death of liver and kidney cells with the development of acute liver and kidney failure. A small part of unchanged NSAIDs and their inactive metabolites are excreted by the kidneys, mainly by tubular secretion, and also with bile. Some of them (indomethacin, oxicams) are reabsorbed in the gastrointestinal tract, which can lead to an increase in their concentration in the

blood. Among NSAIDs, drugs with a short and long half-life can be distinguished (Table 21.3).

**Table 21.3. Half-life of various NSAIDs**

| Short period of half-removal | | Long period of half-removal | |
|---|---|---|---|
| NSAIDs | $T_{1/2}$ (hour) | NSAIDs | $T_{1/2}$ (hour) |
| Acetylsalicylic acid | 0,25 | Celecoxib | 10-12 |
| Diclofenac | 1,1 | Naproxen | 14 |
| Ketoprofen | 1,8 | Meloxicam | 20 |
| Paracetamol | 2,0 | | |
| Ibuprofen | 2,1 | | |
| Lornoxicam | 4,0 | | |
| Ketorolac | 5-6 | | |

Drugs with a shorter half-life require more frequent dosing (with the exception of special retard forms). When using drugs with a longer half-life, the risk of adverse effects increases, especially in elderly patients with hypoalbuminemia, liver and kidney diseases.

**Unwanted actions.**

NSAIDs are a group of drugs that often cause a variety of undesirable effects. Their significance is determined, first of all, by the high frequency of NSAID use. Among the risk factors for the development of undesirable effects of NSAIDs are:

- Elderly and senile age.
- Peptic ulcer in history.
- Intestinal diseases.
- Diseases of the liver.
- Diseases of the kidneys.
- Bronchial asthma.
- Congestive heart failure.
- Chronic alcohol intoxication.
- Diseases of the blood.
- Taking drugs with which NSAIDs interact.
- Lactation.

Damage to the mucous membrane of the stomach and intestines (NSAID-gastropathy and NSAID-enteropathy) is one of the most common adverse effects of NSAIDs.

- ~ Causes 10-15% of acute bleeding from the upper GI tract.
- ~ Leads to total mucosal damage.
- ~ In 60% of cases, gastrointestinal bleeding is complicated.
- ~ Leads to the development of acute erosive and ulcerative lesions of the stomach, occurs in 80 - 90% of patients in intensive care units

Two types of undesirable effects of NSAIDs on the gastrointestinal mucosa can be distinguished:

1) Direct damage to the mucous membrane with a drug located in the lumen of the gastrointestinal tract - the so-called "pill" gastritis, zeophagitis, heartburn, discomfort in the epigastrium. Their development can be avoided by prescribing parenteral or rectal forms of NSAIDs, as well as enteric or instant tablets, recommending that regular tablets be chewed and washed down with plenty of water.

2) Development of acute erosions and ulcers of the stomach and duodenal bulb as a result of blockade of PG synthesis in the mucosa of the gastrointestinal tract by a medicinal substance, delivered to the mucous membrane with blood (resorptive effect). The route of administration does not affect the incidence of this type of adverse event. They are characterized by a latent course, absence of pain, dyspeptic syndromes. Every year, 1-2% of patients regularly receiving NSAIDs are hospitalized due to gastrointestinal bleeding and perforation. Mortality among them reaches 10%. H2-histamine receptor blockers and antacids do not prevent these complications. Synthetic analogue of PG (misoprostol) reduces the risk of developing NSAID gastropathy by about 50%, but it itself can cause undesirable effects from the gastrointestinal tract in the form of abdominal pain, nausea, vomiting, diarrhea, constipation, flatulence. Selective COX-2 inhibitors have a significantly lower risk of developing gastropathy, which makes these drugs the drugs of choice in the treatment of patients at risk: Risk factors for the development of NSAID-gastroduadenopathies:

- ~ elderly and senile age;
- ~ history of peptic ulcers;
- ~ gastrointestinal bleeding or perforation of the gastrointestinal tract in history;
- ~ women;
- ~ simultaneous use of GCS or two NSAIDs;
- ~ high doses of NSAIDs;

- ~ combined use of anticoagulants;
- ~ smoking;
- ~ alcohol consumption.

For the timely detection of gastroduadenopathies, patients systematically receiving NSAIDs should undergo gastroscopy every six months.

Practical ways to overcome gastrotoxicity without stopping NSAIDs:

- ~ therapy with gastrocytoprotectors and antacids (sucralfate, De-nol, maalox, almagel, misoprostol) during NSAID therapy;
- ~ therapy with drugs that block the synthesis of HCl in the stomach (proton pump inhibitors, H2 blockers);
- ~ the use of special dosage forms of acetylsalicylic acid for antiplatelet therapy (enteric forms of aspirin - thrombo-ACS or tablets containing an acid buffer -Cardiomagnyl);
- ~ using the features of the pharmacokinetics of NSAIDs (ibuprofen, lornoxicam);
- ~ use of selective COX2 inhibitors (nimesulide, meloxicam, celecoxib).

*Nephrotoxic action can be realized in different ways.*

1) Direct damaging effect of NSAIDs on the renal parenchyma with the development of interstitial nephritis, necrosis of the renal papillae, renal failure ("analgesic nephropathy"). This was especially evident in the example of phenacetin, nephrotoxic effect of which was the reason for the prohibition of its use. Perhaps the development of acute allergic interstitial nephritis.

2) The blockade of PG synthesis causes a violation of renal blood flow and, as a result, renal ischemia, a decrease in renal filtration, and the development of renal failure. This PD has been described with indomethacin, phenylbutazone, ketorol, and possibly with other NSAIDs. Described the development of renal failure when using a gel containing piroxicam to relieve pain in the shoulder.

Risk factors for the development of NSAID nephrotoxicity:

- ~ Elderly and senile age.
- ~ History of kidney disease.
- ~ Dehydration.
- ~ Decrease in the volume of circulating fluid.

~ Long-term use of NSAIDs and their combination.

*Hematotoxicity*. The toxic effect on the bone marrow is manifested by the development of agranulocytosis, aplastic anemia, and cytopenias. It is most characteristic of pyrazolone and pyrazolidine derivatives: metamizole sodium (analgin, dipyrone, baralgin), phenylbutazone (butadione), aminophenazone (amidopyrine). According to a Swedish study, the incidence of agranulocytosis when taking metamizole sodium is 1 in 1700 prescriptions. Severity and high danger to life complications have served as the basis for the prohibition or significant restriction of the use of these NSAIDs in a number of countries.

*Hepatotoxicity*. The possible hepatotoxic effect of paracetamol has already been mentioned above. This is usually observed with an overdose of drugs in the case of taking 10 or more grams per day with the maximum allowable daily dose for adults - 4 g. At the same time, there are factors that increase the risk of developing hepatotoxicity, which can lead to a narrowing of the therapeutic range, the development of a relative overdose: alcohol consumption, underlying liver dysfunction, concomitant use of hepatotoxic drugs, unbalanced diet and starvation. Toxic symptoms with an absolute or relative overdose of paracetamol appear after 1-2 days. Patients are subject to urgent hospitalization. At early terms they are prescribed antidotes (activated charcoal).

Specific treatment involves the introduction of glutathione precursors containing a thiol group:

~ in severe cases, acetylcysteine is administered intravenously - 140 mg / kg in the first injection, and then 70 mg / kg every 4 hours (total amount 300 mg / kg for 20 hours);
~ in mild cases, methionine 2.5 g is administered orally every 4 hours until a total dose of 10 g is reached.

Other NSAIDs cause liver damage much less frequently than paracetamol. While taking NSAIDs, a transient increase in the activity of liver enzymes in the blood is possible.

*Allergic reactions* in the form of various skin manifestations, anaphylactic reactions are more often observed when taking pyrazolones and pyrazolidines.

*Broncho-obstruction* associated with the blockade of the synthesis of bronchodilating PGs and allergic mechanisms often develops when taking acetylsalicylic acid, but is possible against the background of the use of other NSAIDs, except for paracetamol. Patients with bronchial asthma are at risk, and the appointment of NSAIDs requires special care and control. Acetylsalicylic acid is contraindicated for them.

*Stomatitis* develops when taking any NSAID. The frequency and severity of damage to the oral mucosa depends on the duration of taking NSAIDs.

*Reye's syndrome* - acute hepatic encephalopathy can develop in children with a viral infection while taking acetylsalicylic acid.

*Proctitis, exacerbation of hemorrhoids* can be observed when using rectal forms of NSAIDs.

*Mental disorders* when taking NSAIDs can manifest as hallucinations, confusion (most often while taking indomethacin, up to 1.5-4% of cases, which is associated with a high degree of penetration of the drug into the CNS). Perhaps a transient decrease in hearing acuity when taking acetylsalicylic acid, indomethacin, ibuprofen and drugs of the pyrazolone group.

*The formation of methemoglobin and hemolysis* occur under the influence of paracetamol.

Rare adverse effects of NSAIDs include the development of colitis when taking mefenamic acid, hearing impairment and pulmonary edema when taking salicylates, the development of autoimmune syndromes when taking phenylbutazone, ibuprofen, neurological and mental disorders when taking indomethacin, sialoadenitis when taking phenylbutazone.

**Table 21.4. Drug interactions NSAIDs**

| Drug | NSAIDs | Effect |
|---|---|---|
| Aluminum-containing antacids | All NSAIDs | Decreasing of NSAIDs bioavailability |
| Prokinetics | All NSAIDs | Increasing speed of NSAIDs absorption |
| Indirect anticoagulants | Acetylsalicylic acid, ketorolac, possibly other NSAIDs | Displacement of anticoagulants from bonds with plasma proteins, increasing of its concentration and increasing risk of bleeding |
| Oral hypoglycemic medication | Acetylsalicylic acid, ketorolac, possibly other NSAIDs | Displacement of hypoglycemic medication from bonds with plasma proteins, increasing of its concentration and increasing risk of hypoglycemia |

| | | |
|---|---|---|
| Digoxin | Acetylsalicylic acid, possibly other NSAIDs | Increasing concentration of digoxin in the blood, risk of development of digitalis intoxication |
| Beta-adrenoreceptor blockers | All NSAIDs | Decreasing of hypotensive effect |
| ACE inhibitors | All NSAIDs | Decreasing of hypotensive effect, hyperkalemia |
| Diuretics | All NSAIDs | Decreasing diuretic and hypotensive effect, hyperkalemia, increasing of nephrotoxicity |
| Aminoglycosides | All NSAIDs | An increased risk of developing nephro- and ototoxicity |
| Fluoroquinolones | All NSAIDs | Increased risk of development of headaches, sleep disturbances, convulsive syndrome |
| Fluconazole | Celecoxib | Increased $T_{1/2}$ and celecoxib concentration in the blood |
| Opioids | All NSAIDs | Increased painkilling effect |

**Food interactions**. Most NSAIDs are weak acidstherefore, food slows down their absorption without significantly affecting bioavailability. Food intake increases the bioavailability of celecoxib. Aminophenazone (amidopyrine), when interacting with food nitrites, can form carcinogenic compounds.

**Contraindications**

1. Individual intolerance to the drug in history.
2. Exacerbation of peptic ulcer (except for paracetamol).
3. Pregnancy (except paracetamol).

With extreme caution, NSAIDs should be used in patients at risk, and with regular use, carefully monitor the condition of patients.

**Clinical features of the use of NSAIDs.**

*Use during pregnancy*. In general, the use of NSAIDs during pregnancy should be avoided.

By inhibiting the synthesis of PG in the uterus, which is especially enhanced a few hours before delivery, NSAIDs can lengthen the period of pregnancy and childbirth. NSAIDs help close the ductus arteriosus in the fetus.

Acetylsalicylic acid is undesirable for use in the third trimester of pregnancy, not only because of the possible delay in labor and the risk of premature closure of the arterial (botal) duct, but also because of the increased risk of hemorrhages during childbirth. High doses of acetylsalicylic acid can cause the development of pulmonary hypertension and kernicterus in the newborn. Ketorol is not used in pregnant women. There are no data on adverse effects of paracetamol in pregnant women.

*Use in lactation*. NSAIDs pass into breast milk and are not recommended during lactation. When NSAIDs are used by the mother, the development of metabolic syndrome in infants and the appearance of skin rashes are described, and when indomethacin is taken, convulsions are described. Nursing mothers may use paracetamol.

*Use in children*. Paracetamol is one of the safest drugs and is widely used in children. At the age of up to 3 months, the drug is used at a dose of 10 mg / kg(only as prescribed by a doctor), from 3 months to a year - at a dose of 24-120 mg, from 1 to 5 years - 120-240 mg, from 6 to 12 years - 240 - 500 mg. If necessary, the drug can be repeated every 4-6 hours, up to a maximum of 4 times a day. Course intake should not exceed 3 days.

Ibuprofen for pain and fever in children under 12 years is used with caution at a dose of 10-20 mg / kg per day for 3 doses, its use is not recommended for body weight less than 7 kg.

The safety of ketoprofen, oxicam, celecoxib in children under 15 years of age has not been established.

Acetylsalicylic acid is not used in children under 12 years of age due to the risk of developing Reye's syndrome.

Ketorolac is not recommended for use in children under 16 years of age.

*Prescription and dosage*. The anti-inflammatory effect develops after 10–14

days of regular intake and lags behind the painkiller observed already in the first hours. Sensitivity to the anti-inflammatory action of NSAIDs varies widely, so NSAIDs are selected individually for each patient. As a first-line drug, NSAIDs with a low risk of developing unwanted effects are used. Start with the lowest recommended doses with a gradual increase until the maximum possible therapeutic effect is achieved with constant monitoring of the safety of treatment. With an anti-inflammatory purpose, NSAIDs are prescribed after meals. For a quick analgesic or antipyretic effect, they are taken on an empty stomach for 30 minutes before or 2 hours after a meal with ½–1 glass of water. After receiving within 15 minutes, it is advisable not to lie down in order to prevent esophagitis.

Most NSAIDs are taken 2-3 times a day; depending on the time of maximum severity of symptoms, it is possible to change the regimen of administration. Preparations with a long half-life (oxicam, celecoxib) and retard forms are taken 1-2 times a day.

The simultaneous use of two NSAIDs does not increase the effectiveness of treatment, but increases the risk of developing unwanted effects. An exception is the combination of any NSAID with paracetamol, which enhances the analgesic effect. A combination of high-speed and retard forms of NSAIDs is possible.

Metamizole sodium is one of the most effective analgesics. It is widely used in Russia and is part of OTC combined painkillers. At the same time, the high risk of developing severe life-threatening complications requires limitation and special care in its use, and also monitoring the composition of peripheral blood.

Phenacetin, aminophenazone, as well as any combination of these drugs, for example, a combination of aminophenazone with phenylbutazone (rheopyrin, etc.), due to the high risk of developing severe adverse effects, should not be used.

Phenylbutazone, indomethacin remain reserve drugs for the treatment of a number of rheumatic diseases under strict medical supervision and should not be used in general medical practice.

**Drug**

*Acetylsalicylic acid* (aspirin) is the oldest of the NSAIDs. Aspirin is a trademark of acetylsalicylic acid, proposed by the first manufacturer of the drug, the Bayer company (Germany). Over time, in most countries of the world, it has been transformed into a generic one.

Pharmacodynamics of aspirin depends on the *daily dose*: in small doses (30-325 mg) it causes inhibition of platelet aggregation; in medium (1.5-2 g) - analgesic and antipyretic effect; in large (4-6 g) - anti-inflammatory.

Aspirin is well absorbed from the gastrointestinal tract. Absorption of aspirin is enhanced by crushing the tablet and taking it with warm water, as well as by using "effervescent" tablets, which are dissolved in water before taking. The half-life of aspirin is only 15-20 minutes. Under the action of esterases of the gastric mucosa, liver and blood, salicylate is cleaved from aspirin, which has the main pharmacological activity. The maximum concentration of salicylate in the blood develops 2 hours after taking aspirin, its half-life is 4-6 hours. It is metabolized in the liver, excreted in the urine, and with an increase in the pH of the urine (for example, in the case of the appointment of antacids), excretion increases.

The most specific adverse reactions with aspirin are gastrotoxicity (erosions, ulcers, etc.), increased bleeding, hypersensitivity reactions and Reye's syndrome.

Increased bleeding and prolongation of bleeding time are due to an irreversible violation of platelet aggregation. Normal coagulation rates are restored only 7-10 days after the formation of new platelets. Therefore, aspirin should not be used in patients with a tendency to bleed (hemophilia, hemorrhagic diathesis).

Hypersensitivity reactions can be manifested by skin rash, bronchospasm.

There is a special nosological form - the Fernand-Vidal syndrome ("aspirin triad"): a combination of nasal polyposis and / or paranasal sinuses, bronchial asthma and complete aspirin intolerance. Therefore, aspirin (and other NSAIDs) should be used with great caution in patients with asthma.

Reye's syndrome develops when aspirin is prescribed to children with viral infections(influenza, chickenpox, etc.). It presents with severe encephalopathy, cerebral edema, and liver damage that occurs without jaundice, but with high levels of cholesterol and liver enzymes. Gives very high lethality (up to 80%). Therefore, aspirin should not be used for ARVI in children of the first 12 years of life.

*Overdose* (poisoning) in mild cases is manifested by symptoms "salicylism": tinnitus, stupor, headache, visual disturbances, sometimes nausea and vomiting. With severe intoxication, disorders of the central nervous system and water-electrolyte metabolism develop. There is shortness of breath, respiratory alkalosis and metabolic acidosis, polyuria, hyperthermia, dehydration. Heart failure, pulmonary edema may develop. *Help measures*: gastric lavage using activated charcoal, drinking plenty of fluids (milk, juice), infusion therapy(in / in 0.9% sodium chloride and 10% glucose in a ratio of 1: 2), with collapse - in / in the introduction of colloidal solutions, with acidosis - in / in the introduction of sodium bicarbonate (under the control of blood pH), with hypokalemia - intravenous potassium chloride, physical cooling with water (but not alcohol!), hemosorption, exchange transfusion, with renal failure - hemodialysis.

Aspirin is widely used as an analgesic for postoperative toothache. The effect is dose-dependent, that is, 1000-1200 mg provide more pronounced analgesia than 500-600 mg. Since postoperative toothache persists for a short time, the need for aspirin or other analgesics usually does not exceed 1-2 days after the manipulation. Prophylactic use of aspirin prior to tooth extraction or other manipulation is associated with an

increased risk of postoperative bleeding. The sometimes practiced local use of aspirin (or other NSAIDs) in the form of an application of a tablet “on a sore tooth” has no basis, since the effectiveness of such use has not been objectively proven and, at the same time, it can lead to severe erosive and ulcerative lesions. buccal mucosa or gums.

Aspirin is also used for headache and musculoskeletal pain, as an antipyretic (at body temperature above 38.5-39oC), antiplatelet agent, and rheumatic diseases.

*Diclofenac* (Voltaren, Dicloran, Ortofen) - tablets 0.025 g; injection(ampoules) 2.5%, 3.0 ml; ointment (tubes) 2% 30 g.

One of the most widely used NSAIDs. It has a powerful and rapid analgesic effect, as well as a pronounced anti-inflammatory effect.

It can be used both inside and intramuscularly.

The maximum concentration in the blood develops 0.5-2 hours after ingestion and 10-30 minutes after intramuscular injection. The half-life is 1.5-2 hours.

Diclofenac is generally well tolerated, but with prolonged use, a negative effect on the gastrointestinal tract and liver is possible, therefore, appropriate clinical and laboratory monitoring is necessary.

In dentistry, diclofenac can be used to relieve acute postoperative toothache. In addition, it is widely used for musculoskeletal pain and rheumatology.

*Ibuprofen* (Brufen, Nurofen) - tablets of 0.2 g; oral suspension (vials according to 100ml) 0.1g/5ml.

It is characterized by a pronounced analgesic and antipyretic effect. In terms of the degree of analgesic effect, 200 mg of ibuprofen is approximately equivalent to 650 mg of aspirin and paracetamol. The strength of the anti-inflammatory effect is inferior to diclofenac.

The advantage of the drug is good tolerability, relatively rare development of adverse reactions. The maximum concentration in the blood develops 1-2 hours after ingestion.

It is rapidly metabolized and excreted from the body. The half-life is about 2 hours.

It is widely used as an analgesic both in dentistry and in other areas of medicine, including for over-the-counter dispensing.

*Lornoxicam* (xefocam) - tablets 0.004 and 0.008 g; powder for solution for injection (vials) 0.008 g complete with a solvent.

Representative of the oxycam group. It has a pronounced analgesic and anti-inflammatory effect. One of the possible mechanisms of the analgesic effect is an increase in the level of -endorphins in the central nervous system. Lornoxicam is less gastrotoxic than the “first generation” oxicams (piroxicam). is a non-steroidal anti-inflammatory drug (NSAID) with a pronounced analgesic effect. The mechanism of

action of lornoxicam is based on the inhibition of prostaglandin synthesis due to a balanced inhibition of the activity of cyclooxygenase-1 and cyclooxygenase-2 isoenzymes. Inhibition of the activity of cyclooxygenases does not cause an increase in the production of leukotrienes. Lornoxicam does not have an opiate-like effect on the central nervous system and therefore does not depress respiration, nor does it cause constipation and miotic effects.

Quickly and almost completely absorbed in the gastrointestinal tract. Food reduces the bioavailability of lornoxicam by 20%. Maximum plasma concentrations are observed 1-2 hours after ingestion and 15 minutes after intramuscular administration.

The half-life is 3-5 hours.

It can be used for pains of various localization, including in dentistry. The efficacy and safety of the drug in children under 18 years of age has not been studied.

*Ketorolac* (ketalgin, ketanov, ketorol) - tablets 0.01 g; injection (ampoules, syringes) 3% 1 ml. It is used for pain syndrome of moderate and severe degree (postoperative pain, trauma).

It has a powerful analgesic effect, in terms of which it surpasses many other NSAIDs and approaches opioids (30 mg of ketorolac administered intramuscularly is approximately equivalent to 12 mg of morphine).

Almost completely and quickly absorbed in the digestive tract. The maximum concentration in the blood develops 35 minutes after ingestion and 50 minutes after intramuscular injection. The half-life is 5-6 hours. Of the adverse reactions, gastrotoxicity and increased bleeding due to the antiaggregatory effect of ketorolac are most often noted.

In this regard, the course of prescribing the drug should not exceed 7 days, and use in the elderly should be limited.

In dentistry, ketorolac can be used to quickly relieve postoperative pain. It is also used for pains of other localization.

In severe pain syndrome, it can be combined with opioid analgesics, which allows you to reduce the dose of the latter. Do not use ketorolac for sedation and maintenance anesthesia during operations. Efficacy and safety in children under 16 years has not been established.

*Ketoprofen* (artrosilene, ketonal, oki, oruvel) - tablets 0.1 g; delayed release tablets (retard) 0.15 g, 0.2 g; capsules 0.05 g; prolonged capsules 0.32 g; suppositories 0.1 g; granules (sachets) 0.08 g; injection solution (ampoules) 5% and 8% 2 ml; rinse solution (bottle with dispenser injector) 150 ml: 0.16 g/10 ml; gel (tubes) for external use 2.5%, 30 and 60g.

*Meloxicam* (Movalis) - tablets 0.0075 g and 0.015 g; suppositories 0.015 g

*Paracetamol* (panadol, calpol, efferalgan) - tablets 0.5 g; soluble tablets 0.5 g; solution and suspension for oral administration (bottles) 70 and 100 ml: 0.12 g / 5 ml; rectal suppositories 0.05, 0.1, 0.125, 0.25, 0.5 g.

*Choline salicylate* (mundizal gel, cholisal) - gel for treating the oral cavity (tubes) 8 g, 10 g: 0.871 g choline salicylate + cetalkonium chloride (antiseptic) / 1 g. Apply 3-4 once a day before meals and at bedtime. Gel in the amount of 1 cm for adults and children over 2 years old and in the amount of 0.5 cm for children from 4 months. up to 2 years, gently rubbed into the affected area of the mucosa. In case of periodontal diseases, the drug is injected into the gum pockets 1-2 times a day. Perhaps a burning sensation at the site of application. Only a small part of the administered dose is absorbed from the oral mucosa and swallowed with saliva, however, with a significant overdose, the pharmacological effects of other anti-inflammatory, antipyretic and analgesic drugs may be enhanced. No adverse effects of the drug in pregnant women and lactation have been described.

*Celecoxib* (Celebrex) - capsules 0.1 and 0.2 g.

They have a pronounced anti-inflammatory and analgesic effect. As well as nimesulide, they are selective inhibitors of COX-2, and therefore rarely cause unwanted reactions from the gastrointestinal tract. Sometimes there is a headache, dizziness, sleep disturbances, rashes, rhinitis phenomena. No nephrotoxic reactions registered.

So far, they have been used only in rheumatoid arthritis and osteoarthritis. There are no official indications for use in dentistry yet, although in a short-term study in postoperative toothache, celecoxib showed high analgesic activity.

Given the prospects of this direction, in recent years, new analgesics have been developed that selectively inhibit COX-2. In particular, clinical trials of *parecoxib* (for parenteral administration) and valdecoxib (for oral administration), the purpose of which is to evaluate the analgesic effectiveness of these drugs for postoperative pain.

## Control questions

1. For NSAIDs, all statements are correct except:

a) decrease in elevated body temperature
b) analgesic effect is weaker than that of opioids
c) anti-inflammatory effect is stronger than that of glucocorticoids
d) do not inhibit the respiratory center
e) are well absorbed in the gastrointestinal tract

2. What are the most common side effects of NSAIDs?

a) Immunopathic.
b) Gastropathic and ulcerogenic.
c) Ototoxic.
d) Neurotoxic.
e) Cardiodepressive.

3. Which statement is incorrect about NSAIDs?

a) Rapidly absorbed when taken orally.
b) Significantly associated with plasma proteins.
c) Inhibit COX.
d) Destroyed during the primary passage through the liver.
e) They have an ulcerogenic effect.

4. Which NSAID belongs to the group of selective COX inhibitors?

a) Acetylsalicylic acid.
b) Ibuprofen.
c) Celecoxib.
d) Diclofenac.
e) Ketoprofen.

5. Which of the listed NSAIDs has the highest hematotoxicity?

a) Acetylsalicylic acid.
b) Metamizole sodium.
c) Ketoprofen.
d) Meloxicam.
e) Paracetamol.

6. When should ketorolac be used with extreme caution and with reduced dose?

a) In the elderly and senile age.
b) In chronic bronchitis.
c) With coronary artery disease.
d) With the simultaneous use of digoxin.
e) After local anesthesia.

7. For aspirin, all statements are correct except:

a) dose-dependent effect
b) may cause Reye's syndrome
c) safe in patients with bronchial asthma
d) increases the risk of bleeding
e) high gastrotoxicity

8. What NSAID is used as an antiplatelet agent?

a) Acetylsalicylic acid.
b) Metamizole sodium.
c) Piroxicam.
d) Choline salicylate.
e) Ibuprofen.

9. Which of the following effects do NSAIDs not have?

a) Anti-inflammatory.
b) Painkillers.

c) Immunomodulatory.
d) Antipyretic.
e) Ulcerogenic.

10. NSAIDs are characterized by all of the following drug interactions except

a) Sedatives enhance the analgesic effect of NSAIDs
b) NSAIDs weaken the effect of diuretics
c) NSAIDs enhance the effect of anticoagulants
d) NSAIDs weaken the effect of oral hypoglycemic agents
e) Antacids impair the absorption of NSAIDs in the gastrointestinal tract

# Chapter 22 Antihistamines

*The group of antihistamines* consists of drugs that prevent the development of the effects of histamine by blocking H1 receptors (H1-blockers or H1-antagonists). Histamine, this most important mediator of various physiological and pathological processes in the body, was chemically synthesized in 1907.

Subsequently, it was isolated from animal and human tissues (Windaus A., Vogt W.). Even later, its functions were determined: gastric secretion, neurotransmitter function in the central nervous system, allergic reactions, inflammation, etc. Almost 20 years later, in 1936, the first substances with antihistamine activity were created (Bovet D., Staub A.).

And already in the 60s, the heterogeneity of histamine receptors in the body was proved and three of their subtypes were identified: H1, H2 and H3, differing in structure, localization and physiological effects arising from their activation and blockade. Since that time, an active period of synthesis and clinical testing of various antihistamines begins.

Numerous studies have shown that histamine, acting on the receptors of the respiratory system, eyes and skin, causes the characteristic symptoms of allergies, and antihistamines that selectively block H1-type receptors are able to prevent and stop them. This chapter discusses just such commonly known as antihistamines or antihistamines.

**Indications for use in dentistry**:

a) relief of acute allergic reactions of a mild degree;
b) prevention and treatment of chronic recurrent allergic diseases.

*Classification of antihistamines*. Depending on the degree of selectivity and severity of affinity for H1 receptors, the duration of the blockade, features of pharmacokinetics and undesirable effects distinguish three generations of antihistamines (Table 22.1). First-generation drugs are also called sedatives (according to the dominant undesirable effect), in contrast to second-generation non-sedative drugs. At present, it is customary to single out the third generation: it includes fundamentally new drugs - active metabolites, revealing, in addition to the highest antihistamine activity, the absence of a sedative effect and the cardiotoxic effect characteristic of second-generation drugs.

In addition, according to the chemical structure (depending on the X-bond), antihistamines are divided into several groups (ethanolamines, ethylenediamines, alkylamines, derivatives of alphacarboline, quinuclidine, phenothiazine, piperazine and piperidine).

**Table 22.1. Antihistamines**

| I generation | II generation | III generation |
|---|---|---|
| Diphenhydramine (diphenhydramine, benadryl, allergic), Clemastine (tavegil), Doxylamine (decaprine, donormil), Diphenylpyralin, Bromodifenhydramine, Dimenhydrinate (Dedalone, dramamin), Chloropyramine (suprastin), Brompheniramine, Chloropheniramine, Dexchlorpheniramine, Pheniramine (avil), Mebhydrolin (diazolin), Quifenadine (Phencarol), Sequifenadine (bicarfen), Promethazine (Phenergan, diprazine, pipolfen), Trimeprazine (teralen), Oxomemazine, Alimemazine, Cyclizine, Hydroxyzine (atarax), Meclizine (bonin), Cyproheptadine (peritol) | Acrivastine (semprex), Astemizol (gismanal), Dimetinden (Fenistil), Oksatomide (tinset), Terfenadine (bronal, histadin), Azelastine (allergodil), Levocabastin (Histimet), Mizolastin, Loratadine (Claritin), Epinastin (alesion), Ebastin (Kestin), Bamipin (soventol) | Cetirizine (Zyrtec), Fexofenadine (Telfast), Desloratadine (erius) |

According to their chemical structure, most antihistamines are classified as fat-soluble amines, which have similar structure. Core (R1) represented by an aromatic and/or heterocyclic group and linked by a nitrogen, oxygen or carbon (X) molecule to an amino group. The core determines the severity of antihistamine activity and some of the properties of the substance. Knowing its composition, one can predict the strength of the drug and its effects, such as the ability to penetrate the blood-brain barrier.

**Mechanism of action and pharmacodynamic effects**.

Most H1 blockers are *competitive* histamine antagonists. The exceptions are terfenadine (in doses exceeding therapeutic) and astemizole (already in therapeutic doses), which are very slowly released from the connection with H1 receptors and therefore exhibit the properties of *non-competitive* antagonists.

H1 receptor blockers are not able to displace histamine from an already formed connection with the receptor, but only block free ones, since they have a lower affinity for specific receptors than histamine itself and, therefore, are more effective in preventing allergic reactions than in their relief.

Antihistamines have varying degrees of selectivity for different histamine receptor subtypes, but most of them clinically significantly eliminate the effects of histamine due to activation of H1 receptors. The impact on other subtypes is much less or almost non-existent.

Many drugs of this group, especially the first generation, which have the weakest affinity for H1 receptors, are already capable of blocking receptors of other physiological mediators (serotonin, m-cholinergic, adrenal), which causes a number of additional effects, in most cases undesirable. Preparations of the 1st generation also block sodium channels and, due to this, have a pronounced local anesthetic effect.

There is evidence that third-generation antihistamines not only block H1 receptors, but to some extent they are polyfunctional anti-allergic agents, since they are additionally able to stabilize mast cells, which are targets for allergies, preventing their activation and involvement in the allergic process.

**Main therapeutic effects**. Antihistamines have a wide range of therapeutic effects, since histamine is a mediator of a large number of reactions in the human body. It accumulates and is stored in mast cell granules, basophils and platelets and is released from them under the action of immunological and non-immunological stimuli. In addition, histamine acts as a neurotransmitter that performs neuroendocrine control, regulation of the function of the cardiovascular system, thermoregulation, and the process of excitation. To date, three subtypes of histamine-sensitive receptors (H-receptors) have been identified, activation of which leads to different effects.

Histamine is the most important mediator of allergic and anaphylactoid (pseudo-allergic) reactions. In these reactions, the effects of histamine are realized through the action on H1 receptors. The release of histamine from mast cells and basophils under the influence of provoking factors leads to a decrease in blood pressure, tachycardia, bronchial obstruction, characteristic skin manifestationsedema (blisters), fever and flushing of the skin (the so-called "triple" response), skin itching.

At pregnant women, due to an increase in the tone of the muscles of the uterus, it is possible to terminate the pregnancy. In addition to histamine, bradykinin, prostaglandins, leukotrienes, platelet activating factor and other mediators also play an

important role in the pathogenesis of allergic reactions. Antihistamines are used in the treatment of acute and chronic allergic diseases and pseudo-allergic reactions. Due to the blockade of H1 receptors, they eliminate edema, hyperthermia and hyperemia of tissues, skin itching, vascular effects, bronchospasm. Their ability to eliminate bronchospasm caused by histamine is not essential in the treatment of patients with bronchial asthma, where many other mediators and biologically active substances are involved in the pathogenetic mechanism. Moreover, the thickening of sputum observed with the use of many of them can lead to aggravation of bronchial obstruction.

The concomitant blockade of not only histamine, but a number of other receptors, which is most pronounced in drugs of the first generation, is manifested by a certain range of undesirable effects in relation to the central nervous system, cardiovascular, urinary, digestive systems.

The following summarizes the features characteristic of antihistamines of various generations:

**First generation antihistamines (sedatives):**

- Pronounced sedative effect, determined by the fact that easily dissolving in lipids, well penetrate the blood-brain barrier and bind to H1-brain receptors. Perhaps thiseffect consists of blocking the central serotonin and acetylcholine receptors. The degree of manifestation of first-generation sedation varies with different drugs and patients from moderate to severe and increases when combined with alcohol and psychotropic drugs. Some of them are used as sleeping pills (doxylamine). Rarely, instead of sedation, psychomotor agitation occurs (more often in medium therapeutic doses in children and in high toxic doses in adults). Due to the sedative effect, most drugs should not be used during tasks that require attention. All first-generation drugs potentiate the action of sedative and hypnotic drugs, narcotic and non-narcotic analgesics, monoamine oxidase inhibitors and alcohol.The anxiolytic effect characteristic of hydroxyzine may be due to the suppression of activity in certain areas of the subcortical region of the CNS.
- Atropine-like reactions associated with the anticholinergic properties of drugs are most characteristic of ethanolamines and ethylenediamines. Manifested by dry mouth and nasopharynx, urinary retention, constipation, tachycardia and visual impairment. These properties ensure the effectiveness of the discussed remedies in non-allergic rhinitis. At the same time, they can increase obstruction in bronchial asthma (due to an increase in sputum viscosity), exacerbate glaucoma and lead to infravesical obstruction in prostate adenoma, etc.
- Antiemetic and antiswaying effects are also likely to be associated with the central anticholinergic effect of the drugs. Some antihistamines(diphenhydramine,

promethazine, cyclizine, meclizine) agents reduce the stimulation of vestibular receptors and inhibit the function of the labyrinth, and therefore can be used for motion sickness.

- ~ A number of H1-histamine blockers reduce the symptoms of parkinsonism, which is due to the central inhibition of the effects of acetylcholine.
- ~ Antitussive action is most characteristic of diphenhydramine, it is realized through a direct action on the cough center in the medulla oblongata.
- ~ Antiserotonin effect, characteristic primarily of cyproheptadine, leads to its use in migraine.
- ~ α1-blocking effect with peripheral vasodilation, especially inherent in phenothiazine antihistamines, can lead to a transient decrease in blood pressure in sensitive individuals.
- ~ Local anesthetic (cocaine-like) action is characteristic of most antihistamines (occurs due to a decrease in membrane permeability to sodium ions). Diphenhydramine and promethazine are stronger local anesthetics than novocaine! However, they have systemic quinidine-like effects, manifested by prolongation of the refractory phase and the development of ventricular tachycardia. Tachyphylaxis: decrease in antihistamine activity with long-term use, confirming the need for alternating drugs every 2-3 weeks.
- ~ First generation antihistamines differ from the second generation in the short duration of exposure with a relatively rapid onset of the clinical effect.
- ~ Many drugs are presented in parenteral form.

Some properties of antihistamines of the 1st generation due to the peculiarities of their action are used in the treatment of certain pathologies (migraine, sleep disorders, extrapyramidal disorders, anxiety, motion sickness, etc.) not associated with allergies.

**Second generation antihistamines** (non-sedating). Unlike of the previous generation, they almost do not have sedative and anticholinergic effects, but differ in their selective action on H1 receptors. However, for them, a cardiotoxic effect was noted to varying degrees.

The following properties are the most common for them:

- ~ High specificity and high affinity for H1 receptors with no effect on choline and serotonin receptors.
- ~ Quick onset of clinical effect and duration of action. Prolongation can be achieved due to high protein binding, accumulation of the drug and its metabolites in the body, and delayed elimination.
- ~ Minimal sedative effect when using drugs in therapeutic doses. It is explained by the weak passage of the blood-brain barrier due to the

peculiarities of the structure of these funds. Some particularly sensitive individuals may experience moderate drowsiness, which is rarely the reason for discontinuing the drug.

- ~ Absence of tachyphylaxis with prolonged use.
- ~ The ability to block the potassium channels of the heart muscle, which is associated with prolongation of the QT interval and cardiac arrhythmias. The risk of thisundesirable effect increases with the combination of antihistamines with antifungal (ketoconazole and itraconazole), macrolides(erythromycin and clarithromycin), antidepressants (fluoxetine, sertraline and paroxetine), with the use of grapefruit juice, as well as in patients with severe liver dysfunction.
- ~ Absence of parenteral forms, however, some of them (azelastine, levocabastin, bamipin) are available in the form of forms for topical use.

*Antihistamines of the third generation (metabolites).* Their fundamental difference is that they are active metabolites previous generation antihistamines.

- ~ pharmacological effect does not depend on the individual characteristics of metabolism,
- ~ the absence of clinically significant interactions with drugs that inhibit the activity of the cytochrome P450 system,
- ~ no cardiotoxicity, inability to influence the QT interval,
- ~ polyfunctional effect on the allergic cascade.

**Pharmacokinetics**

*Bioavailability.* All antihistamines when taken orally are well absorbed from the gastrointestinal tract (by 70-95%).

Means of the 1st generation are characterized by a high degree of first pass effect through the liver with the formation of inactive metabolites, and therefore their bioavailability is only about 40%. Antihistamines of the second generation, being "prodrugs", they pass into the active form after oxidation in the liver by the cytochrome P450 system. Their bioavailability reaches 90% or more. In case of violation of hepatic metabolism, exceeding the dose or concomitant administration of drugs, metabolized by the same enzymes, the original substance accumulates in the body and the development of toxic reactions is possible. III generation drugs are developed on the basis of active metabolites of II generation drugs, therefore they are not metabolized. Their

concentration in the blood does not depend on the characteristics of individual metabolism - they have greater stability and reproducibility of the effect.

Distribution and association with proteins. Antihistamines are widely distributed in the body, reaching high concentrations in the liver, lungs, brain, kidneys, spleen, and muscles. Their connection with plasma proteins reaches 83-90%.

The 1st generation drugs penetrate the blood-brain barrier well, while preparations of the 2nd and 3rd generation are much less lipophilic and penetrate into the cerebrospinal fluid to a very small extent (the exception is cetirizine, the concentration of which in the spinal cerebral fluid reaches 10% of the concentration in the blood). Most drugs penetrate well through the placental barrier and into breast milk.

*Metabolism and elimination*. Most antihistamines are metabolized in the liver. The resulting metabolites and the remaining unchanged part of the drug are excreted from the body with urine or through the gastrointestinal tract. In liver failure, their dose should be reduced. Most of the administered dose of cetirizine and acrivostatin is excreted unchanged in the urine, requiring dose reduction in patients with impaired renal function.

The onset of action of 1st generation antihistamines is observed 20-60 minutes after ingestion and lasts 4-6 hours, so they are used 3-4 times a day. The exception is clemastine, which lasts 8-12 (possibly up to 24) hours, and applied 2 times a day. The half-life for drugs of the first generation is 4-10 hours.

The onset of action of II and III generation drugs is observed 1–2 hours after administration and lasts about 20–24 hours. The elimination half-life ranges from 7–8 to 20 hours, andfor astemizole is 5-10 days. These drugs have a long-term effect.

Equilibrium plasma concentrations are reached after 3-5 days from the start of administration. The frequency of taking drugs of the II and III generations is 1-2 times a day. Acrivastatin, with an effect duration of 12 hours, differs among second-generation drugs in a faster onset of effect (onset of action as early as 20–30 minutes after administration), which allows it to be used to stop mild acute allergic reactions. The onset of action of desloratadine is observed 20-30 minutes after ingestion and lasts for 24 hours.

**Unwanted effects**.

*CNS*.

- sedative effect, lethargy, dizziness, ataxia, numbness of the oral mucosa, which are characteristic, first of all, of the first generation drugs and significantly limit their use; of the newer antihistamines, cetirizine has a slight sedative effect.

*The cardiovascular system*.

- ~ decrease in blood pressure due to the adrenolytic effect of drugs (expressed with parenteral administration);
- ~ cardiotoxic effect due to blockade of potassium channels and expressed in a delay in ventricular repolarization, which leads to an increase in the QT interval, expansion of the T wave, the appearance of ventricular extrasystoles and tachycardia (*astemizole* and *terfenadine*, which caused a significant limitation of their use).

*GIT.*

- ~ nausea, epigastric pain, exacerbation of peptic ulcer (diphenhydramine, clemastine); taking drugs after meals prevents the development of dyspeptic symptoms.

*Liver*.

- ~ dysfunction;
- ~ increased levels of enzymes.

*The mucous membrane of the oral cavity*.

- ~ dryness, thickening of saliva, numbness (more pronounced when using drugs 1st generation).

*Drug addiction.*

- ~ may occur with long-term use of first-generation drugs.

*Rare adverse effects*: allergic and anaphylactoid reactions, oppression of hematopoiesis, weight gain (astemizole), galactorrhea (terfenadine).

Some of these and many other undesirable effects are due to the concomitant *m-anticholinergic effect.* Among them are dry mouth, thickening of saliva, bronchial secretions and discharge from the nose, constipation, exacerbation of glaucoma,
violation of the outflow of urine, tremor of the limbs, visual impairment, agitation and insomnia in children of younger age groups and the elderly. These effects are more characteristic of the first generation drugs.

**Drug Interactions**

*Antihistamines of the 1st generation* enhance the action of analgesics, antipyretics, anesthetics, local anesthetics, m-anticholinergics, alcohol. They also potentiate the effects of sleeping pills (at the same time, barbiturates can increase metabolism and weaken the effect of antihistamines), tranquilizers, neuroleptics and other drugs with sedative properties,for example, the sedative effect is increased as a

result of combined use with clonidine. Caffeine reduces their inhibitory effect on the central nervous system. Decreased peristalsis, they increase the absorption of drugs that are slowly absorbed from the gastrointestinal tract, and often impair the absorption of rapidly absorbed drugs (eg, paracetamol).

*Cetirizine*, like the first generation drugs, enhances the effect of drugs, oppressive central nervous system and alcohol; their combined use is contraindicated.

*Second-generation antihistamines*, with the exception of cetirizine, are not combined with potentially hepatoxic drugs.

*Astemizole and terfenadine*, due to the risk of developing ventricular arrhythmias, are not used in conjunction with macrolides (with the exception of spiramycin and azithromycin), ketoconazole, itraconazole, fluoroquinolones, antiarrhythmic and antimalarial drugs, sotalol, i.e. drugs that cause QT prolongation. Their combination with diuretics and other drugs is contraindicated, causing electrolyte disturbances.

*Diphenhydramine and promethazine* are inducers of microsomal liver enzymes and can enhance the biotransformation of drugs metabolized by these enzyme systems, shortening and weakening the effects of these drugs.

**Food interactions.**

Eating impairs the absorption of first-generation antihistamines, therefore, they are prescribed on an empty stomach or 2 hours after a meal.

Eating does not impair the bioavailability of II and III generation antihistamines, but slows down their absorption and lengthens the time to reach maximum blood concentration.

Grapefruit juice increases the plasma concentration of terfenadine.

Patients receiving first-generation antihistamines and cetirizine should not take alcohol, but since the possibility of alcohol interaction with other antihistamines cannot be completely ruled out, the doctor should warn the patient about the possibility of increasing the sedative effect of alcohol while taking any drugs in this group.

**Contraindications:**

- ~ Allergic and anaphylactoid reactions to antihistamines in history.
- ~ Benign prostatic hyperplasia, violation of the outflow of urine, glaucoma (I generation).
- ~ Peptic ulcer in the acute stage (diphenhydramine, chloropyramine).
- ~ Severe liver dysfunction (astemizole, terfenadine).
- ~ Severe renal dysfunction (cetirizine, acrivastatin).
- ~ Porfiry.

**Features of clinical use in various categories of patients**

With extreme caution, antihistamines should be used in patients at risk:

- ~ Younger age groups.
- ~ Elderly and senile age.
- ~ Professions that require concentration.
- ~ Pregnancy and lactation.
- ~ Epilepsy.
- ~ IHD, heart failure, arrhythmias.
- ~ COPD
- ~ Liver diseases.
- ~ Violation of the excretory function of the kidneys (acrivostatin, cetirizine).
- ~ Peptic ulcer of the stomach and duodenum.
- ~ Taking drugs with which there is a risk of unwanted interactions.

*Use during pregnancy*. There is no evidence of teratogenic or embryotoxic effects of antihistamines in humans. Nonetheless, it is recommended to avoid the use of these drugs, especially astemizole, in pregnant women.

*Use in lactation*. Antihistamines pass into breast milk. The appearance of drowsiness in a child is described when the mother takes antihistamines. It is recommended to avoid their use during lactation.

*Use in children*. Children belong tocategories of patients most at risk for the development of undesirable effects of antihistamines. The safety of many of them in children of younger age groups has not been established, therefore, a differential approach should be taken to the choice of medicine for a child, based on recommendations for the use of a particular antihistamine.

**Drugs**

*Diphenhydramine* (diphenhydramine) is a first-generation antihistamine drug, one of the first synthesized H1-blockers. Possesses a pronounced antihistamine, antiemetic, sedative, hypnotic, local anesthetic (when taken orally), antitussive action. With parenteral administration, especially in patients with dehydration, a decrease in blood pressure may be observed. Causes dry mucous membranes thickening of saliva, urinary retention. In patients with focal brain damage, epilepsy can provoke a seizure.

When taken orally, the maximum effect develops after 1 hour, the duration of action is 4-6 hours.

It is used to stop acute allergic reactions of mild severity. It has a significant local anesthetic effect, as a result of which it is sometimes used as an alternative for intolerance to novocaine and lidocaine.

The dose for adults is: inside 30-50 mg 2-3 times a day, the maximum daily dose is 250 mg, a single dose is 100 mg; parenterally - 10-50 mg, the maximum daily dose - 150 mg, single dose - 50 mg. The dose for children inside is: under the age of one year - 2-5 mg, at the age of 2-5 years - 5-15 mg, 6-12 years - 15-30 mg per dose or 1-1.5 mg / kg / day; dose for intramuscular injection - 0.5 mg / kg / day.

Available in tablets of 0.05 g and as a 1% solution for injection in ampoules of 1ml.

*Chlorpyramine* (suprastin) - refers to the drugs of the first generation. Along with a pronounced antihistamine, it has peripheral anticholinergic, antispasmodic action. It has antipruritic, sedative and hypnotic effects. When taken orally, it is quickly and completely absorbed, the maximum concentration in the blood is reached after 2 hours and remains at a therapeutic level of 4-6 hours. It is used for the relief of acute mild allergic reactions, the treatment of chronic and recurrent allergic diseases.

It is used orally (during meals), intramuscularly and intravenously. The dose for adults is: inside - 25 mg 3-4 times a day, maximum - 150mg/day; parenterally - 1-2 ml of a 2% solution. The dose for children inside is: aged 1–12 months - 6.25 mg, from 1 to 6 years - 8.33 mg, 7-14 years 12.5 mg 2-3 times a day (or 1-3g/kg/day); intramuscularly single dose depending on age is 0.5-2.0 ml 2% solution.

Available in tablets of 0.025 g and as a 2% solution for injection in ampoules of 1ml.

*Clemastine* (tavegil) is an antihistamine of the first generation. It has a pronounced antihistamine and weak m-anticholinergic and sedative effects.

When taken orally, it is almost completely absorbed from the gastrointestinal tract. Reaches the maximum concentration in the blood after 2-4 hours. Metabolized in the liver; elimination through the kidneys.

The maximum antihistamine effect develops after 5-7 hours; duration of action - up to 10-12 hours.

It is used for contact dermatitis, acute and chronic eczema, itching, urticaria, angioedema, erythema, nasopharyngitis, vasomotor rhinitis. At parenteral form is used to stop mild acute allergic reactions. When administered orally, the dose for adults and children over 12 years of age is 1 mg 2 times a day; in children 6-12 years old, 0.5-1 mg 2 times a day. In / in a jet or in / m introduces 2mg for adults, children i / m 0.025 mg / kg per day in two divided doses.

Available in tablets of 0.001 g; in the form of syrup in bottles of 60 and 100 ml: 0.67mg/5 ml; in the form of a 0.1% solution for injection in ampoules of 2 ml.

*Quifenadine* (fencarol) - has less antihistamine activity than diphenhydramine, but is also characterized by less penetration through the blood-brain barrier, which determines the lower severity of its sedative properties. In addition, fenkarol not only blocks histamine H1 receptors, but also reduces the content of histamine in tissues. May be used in the development of tolerance to other sedative antihistamines.

*Loratadine* (claritin, clarotadine, loratin) is a second-generation antihistamine. It is used for the treatment and prevention of seasonal and year-round allergic rhinitis, hay fever, allergic conjunctivitis, chronic idiopathic urticaria, pruritic dermatoses, angioedema, allergic reactions to insect bites, pseudo-allergic reactions to histamine liberators. When taken orally, it is rapidly absorbed, the maximum concentration of loratadine in the blood is reached after 1.3 hours, its active metabolite - after 2.5 hours. Their equilibrium concentration in the blood is reached by the 5th day of administration. In elderly patients, in patients with kidney and liver disease, the metabolism and excretion of the drug slow down.

Applied insidebefore meals (food slows down the achievement of maximum concentration). The dose for adults and children over 12 years of age is 10 mg per day. Children from 2 to 12 years is prescribed 5 mg per day. With creatinine clearance less than 30 ml / min, the dose is 5 mg per day or 10 mg every other day.

Available in tablets of 0.01 g; as an oral suspension in vials of 30 and 100 ml: 5 mg/5 ml; as a syrup in vials of 60, 100 and 120 ml: 1 mg/ml.

*Acrivastatin* (semprex) is a second-generation drug. It has a pronounced antihistamine and weak m-anticholinergic and sedative effects. Rapidly absorbed in the gastrointestinal tract, the onset of action after 30 minutes, the maximum - 1-2 hours after administration. Duration of action - 6-12 hours. Used for treatment and prevention seasonal and chronic allergic diseases, may be used for relief of mild acute allergic reactions.

Applied inside. Dose for adults and children from 12 years of age 0.008 g three times a day.

Available in capsules of 0.008 g.

*Desloratadine* (Erius) is a third-generation antihistamine. Renders long-term antihistamine action, without having a sedative effect. Applicable for seasonal allergic rhinitis. When taken orally, it is relatively rapidly absorbed: blood begins to be determined after 30 minutes and reaches a maximum concentration after 3 hours. Almost 90% is metabolized in the liver.

It is used orally, regardless of the meal. Dose for adults and older children 12 years is 5 mg per day. The drug has not been studied in children under 12 years of age.

Available in tablets of 5 mg.

**Control questions**

1. What is unusual for 1st generation antihistamines?

a) high affinity for H1 receptors.
b) sedative effect.
c) anticholinergic action.
d) ability to cause dryness of the oral mucosa.
e) local anesthetic action.

2. Which statement is not true for 2nd generation antihistamines?

a) they are prodrugs.
b) they are metabolized during their first passage through the liver.
c) they are used to prevent seasonal allergic diseases.
d) they cause marked drowsiness.
e) interact with drugs metabolized by the cytochrome P450 system.

3. What is typical for third-generation antihistamines?

a) Do not undergo primary metabolism when passing through the liver.
b) High affinity for H1 receptors.
c) Their action does not depend on the characteristics of individual metabolism.
d) Do not have a sedative effect.
e) All of the above.

4. What drug has a particularly pronounced cardiotoxic effect?

a) Desloratadine.
b) Terfenadine.
c) Cetirizine.
d) Chloropyramine.
e) Acrivastatin

5. What effects of histamine are realized through H1 receptors?

a) Vasodilation.
b) Bronchoconstriction.
c) Stimulation of the secretion of hydrochloric acid.
d) Increased automatism of the sinus node.
e) All of the above.

6. What is a contraindication to prescribing antihistamines?

a) allergic reaction to antihistamines in history.
b) ischemic heart disease.
c) hypertension.
d) lactation.
e) diet containing dairy products.

7. What is a contraindication to the appointment of astemizole?

a) Glaucoma.
b) Benigning of prostatic hyperplasia.
c) Severe liver dysfunction.
d) Severe renal dysfunction.
e) All of the above.

8. What is characteristic of diphenhydramine?

a) Severe sedation.
b) Antitussive action.
c) Antiemetic action.
d) Xerostomia.
e) All of the above.

9. What antihistamine has a half-life of 5–10 days?

a) Chlorpyramine.
b) Akrivastine.
c) Loratadina.

d) Diphenhydramine.
e) Astemizol.

10. What drug is used to stop acute allergic reactions of mild degree of severity?

a) Chlorpyramine.
b) Diphenhydramine.
c) Acrivastatin.
d) All of the above drugs.
e) None of the above drugs.

# Chapter 23. Glucocorticosteroids

*Glucocorticosteroids (GCS) or glucocorticoids* are a group of drugs that include steroid hormones produced in the adrenal cortex, and synthetic drugs that are derivatives of hydrocortisone, the most active natural GCS.

In clinical practice, corticosteroids are used as anti-inflammatory, antiallergic, immunosuppressive agents; in a number of situations, their vasoactive, bronchodilator, decongestant and some other properties are used.

**Indications for use in dentistry:**

a) treatment of non-microbial lesions of the oral mucosa - erythema multiforme exudative, pemphigus, lichen planus, desquamative gingivitis, etc. (locally, for a long time, and in case of severe ulceration of the oral mucosa and systemically);
b) treatment of aphthous stomatitis (locally);
c) treatment of arthritis of the temporomandibular joint (intra-articular with a unilateral process);
d) relief of emergency conditions - acute adrenal insufficiency,
e) anaphylactic shock and other severe allergic reactions, an attack bronchial asthma (systemically).

**Classification**. GCS differ in originnii, by duration of action, according to the severity of the concomitant mineralocorticoid effect, according to the features of the application (topically or systemically).

Natural and synthetic corticosteroids are distinguished by origin (Table 23.1). A very important characteristic of this group of drugs is fluorine substitution, since it is associated with a number of features of pharmacokinetics and pharmacodynamics.

**Table 23.1. Classification of GCS by origin**

| Natural | Synthetic | |
|---|---|---|
| Cortisone<br>Hydrocortisone | A. Non-fluorinated:<br>Prednisolone (mazipredone),<br>Methylprednisolone | B. Fluorinated:<br>Triamcinolone,<br>Dexamethasone,<br>Betamethasone |

GCS have different glucocorticoid activity, different severity of the concomitant mineralocorticoid effect and different duration of action (Table 23.2). You can select means of short, medium and long action. To compare the effects of individual drugs, hydrocortisone is used as a reference drug, the severity of anti-inflammatory (as manifestations of glucocorticoid) and mineralocorticoid effects of which is taken as a unit.

**Table 2. The ratio of anti-inflammatory (glucocorticoid) and mineralocorticoid activity of GCS with different duration of action, applied systemically.**

| Drugs | Activity | |
|---|---|---|
| | Anti-inflammatory | Mineralocorticoid |
| Short term effect | | |
| Cortisone | 0.8 | 1 |
| Hydrocortisone | 1 | 1 |
| Medium term effect | | |
| Prednisolone (mazipredone) | 4 | 0.8 |
| Methylprednisolone | 5 | 0.1 |
| Long term effect | | |
| Triamcinolone | 5 | 0* |
| Dexamethasone | 30 | 0* |
| Betamethasone | 30 | 0* |

* The severity of mineralocorticoid activity is so small that in practical conditions it can be taken as "0".

The strength of the GCS for external use is also a very important characteristic for practice (Table 23.3). When prescribing GCS, certain of their compounds are locally used, which have the least absorption and the greatest severity of local effects.

**Table 23.3. Classification of GCS for external use by activity**

| | |
|---|---|
| Weak | Hydrocortisone (as acetate) 0.1%, 0.25%, 1%, 5% |
| Medium strength | Prednisolone 0.25% and 0.5% |
| Strong | Hydrocortisone (as 17-butyrate) 0.1%<br>Betamethasone (as valerate) 0.1%<br>Triamcinolone (as acetonide) 0.1% |
| Very strong | Clobetasol (as propionate) 0.05% |

**Mechanism of action.**

GCS have a variety of mechanisms of action, the significance of each of which varies with their various effects.

Influencing the function of DNA and RNA, GCS stimulate the formation of lipocortins, possessing anti-edematous action, and one of which inhibits phospholipase-A2, in as a result, the synthesis of prostaglandins and leukotrienes, which play a key role in the development of the inflammatory response, is disrupted. The effects of the GCS are realized not only through the nucleus, but also through membrane and cytoplasmic receptors, which ensures a high rate of development of some of them, especially when high doses of corticosteroids are administered intravenously.

**Clinically significant pharmacodynamic effects.** GCS affect all types of metabolism, and in the first place - on carbohydrate; affect the cardiovascular system, immunity and many other systems and functions. Among the many effects of drugs in this group, the main therapeutic effects can be distinguished (anti-inflammatory, antiallergic, decongestant and some others) and effects that, depending on the situation, are considered either as therapeutic, or as undesirable (immunosuppressive, interaction with the sympathoadrenal system, effect on endocrine functions, etc.).

*Anti-inflammatory action*. GCS inhibit all phases of inflammation. Many factors play a role in their anti-inflammatory action: a violation of the formation of prostaglandins and leukotrienes, stabilization of lysosome membranes, a decrease in capillary permeability, inhibition of the migration of neutrophils and macrophages to the site of inflammation, inhibition of fibroblast proliferation and collagen synthesis, suppression of the formation of cytokines by lymphocytes and macrophages.

*Immunomodulatory and anti-allergic action.* As a result of the suppression of various stages of immunogenesis, GCS have a pronounced immunosuppressive activity: they inhibit the migration of stem cells, the migration of B-cells, the interaction of T- and B-lymphocytes, inhibit the proliferation of lymphoid tissue and cellular immunity. They interfere with the interaction of immunoglobulins with mast cells, macrophages, inhibiting the release of allergic mediators from them.

*Influence on the blood system.* Already after a single dose of CGS, there is a decrease in the number of lymphocytes, monocytes, eosinophils, basophils in the peripheral blood with the simultaneous development of neutrophilic leukocytosis. The maximum changes are noted after 4-6 hours, the restoration of the initial state - after 24 hours. After completing a long course of corticosteroid therapy, changes in the blood may persist for 1–4 weeks. GCS stimulate the formation of red blood cells and platelets.

*Interaction with the sympathoadrenal system*. GCS stimulate the synthesis of adrenoreceptors (both alpha and beta) and increase their sensitivity to catecholamines, which enhances the effect of the latter on various tissues (bronchi, heart, vessels).

*Influence on the cardiovascular system.* GCS enhance not only the effects of catecholamines, but also the pressor effect of angiotensin-II. They maintain the tone of arterioles andmyocardial tension, increase heart rate and cardiac output, increase blood pressure.

*Influence on endocrine functions.* An increase in the level of GCS leads, by a feedback mechanism, to inhibition of the hypothalamic-pituitary-adrenal system (see Fig. 1), expressed in inhibition of the secretion of adrenocorticotropic and other tropic(eg, thyroid-stimulating) hormones. Inhibition is more pronounced with prolonged use of corticosteroids and / or the use of long-acting drugs. GCS reduce the production of sex hormones.

**Influence on metabolism**.

*Carbohydrate metabolism*. By enhancing the absorption of carbohydrates in the gastrointestinal tract, gluconeogenesis in the liver and a decrease in membrane permeability to glucose develops hyperglycemia. Glycosuria and steroid diabetes may develop.

*Protein metabolism*. Due to inhibition of synthesis and increased protein breakdown, especially in the skin, muscle and bone tissues, atrophy of the skin and muscles, muscle weakness, striae, weight loss, hemorrhages, and delayed wound healing develop.

*Fat metabolism*. Multidirectional influence on lipid metabolism in different regions – increased lipolysis in the tissues of the extremities and stimulation of lipogenesis in the tissues of the chest, neck, face, shoulder girdle - leads to a redistribution of subcutaneous adipose tissue according to the cushingoid type.

*Water-electrolyte metabolism and calcium metabolism*. The concomitant mineralocorticoid activity of GCS is manifested by a delay in the body of sodium and water and increased excretion of potassium. Decreased absorption of calcium in the intestine contributes to its release from bone tissue and increased excretion in the urine, resulting in osteoporosis, hypocalcemia and hypercalciuria.

**Pharmacokinetics.**

*Absorption*. GCS are well absorbed in the gastrointestinal tract. The maximum concentration in the blood is reached after 0.5–1.5 hours. Eating somewhat slows down the rate of absorption, but does not reduce its degree.

Injectable forms of GCS are available in the form of various esters:

- ~ succinates, hemisuccinates and phosphates are water-soluble, have a fast and relatively short-term effect; in emergency situations, they are the drugs of choice and are administered intravenously; when administered intramuscularly, the maximum effect develops after 1-2 hours;
- ~ acetates and acetonides are insoluble in water and are finely crystalline suspensions, the action of which develops slowly (in for several hours) and lasts for a long time (several weeks); they are intended for intra- and periarticular administration; when administered intramuscularly, they are slowly absorbed with the onset of action after 1–2 days, with a maximum
- ~ after 4-8 days and duration - up to 4 weeks; administer them intravenously
- ~ it is forbidden.

*Bonding with plasma proteins and distribution in the body*. In the blood plasma, different GCS on 40-95% bind to proteins (transcortin, albumin), creating minimal plasma concentrations of free substance. The free fraction of synthetic drugs is completely distributed in tissues, which explains their higher activity. Penetrate through the placenta, creating high concentrations in the tissues of the fetus, which is especially true for fluorinated corticosteroids.

*Metabolism and elimination*. Cortisone and prednisone in the process of metabolism first turn into active forms - hydrocortisone and prednisolone. In the future, like other corticosteroids, they are metabolized in the liver with the formation of inactive metabolites, and natural faster than synthetic. Fluorinated corticosteroids are metabolized more slowly than all the others.

Excretion of inactive metabolites is carried out by the kidneys. Natural corticosteroids have the smallest T1 / 2, fluorinated drugs - the longest. In renal failure, this parameter does not change, so dose adjustment is not made.

**Unwanted actions.**

With the systemic use of GCS, a wide variety of complications can develop. The risk of their occurrence, as a rule, increases with increasing dose and duration of treatment.

*CNS* - increased appetite, hyperactivity, euphoria, anxiety, depression, psychosis, convulsions, hypertensive-hydrocephalic syndrome.

*GIT*- steroid ulcers of the stomach and intestines, often with bleeding and perforation, esophagitis, pancreatitis, dyspepsia.

*Cardiovascular system and hemostasis* - arterial hypertension, tachycardia, vasculitis, thrombosis.

*Endocrine system* - decreased stress resistance and withdrawal syndrome(due to inhibition of the hypothalamic-pituitary-adrenal system), Cushing's syndrome, hyperglycemia, steroid diabetes, manifestation of latent diabetes, hyperlipidemia, negative nitrogen balance, dys- and amenorrhea, growth retardation and delayed puberty in children.

*Immune system* - suppression of immunogenesis with activation of tuberculosis and other infections - bacterial, viral, fungal (in patients with bronchial asthma, using inhalers with corticosteroids, candidiasis of the oral cavity may develop), an increased risk of superinfections and an atypical course of infectious diseases (“blurring” of the clinical picture).

*Water-electrolyte metabolism* - increased loss of potassium, magnesium, calcium, sodium and water retention, edema.

*Musculoskeletal system* - myopathy, osteoporosis, vertebral compression fractures, other pathological fractures, aseptic necrosis of the femoral head.

*Skin* - hemorrhages, acne, striae, thinning of the skin; atrophy of the skin and subcutaneous tissue with intramuscular injection (the most dangerous is the introduction into the deltoid muscle).

*Regeneration* - a violation of wound healing (in patients receiving corticosteroids, damage to the oral cavity heals slowly, infections develop more often, and the mucosa as a whole is more susceptible to trauma, which must be taken into account when performing dental procedures).

*Eyes* - glaucoma (with possible exophthalmos), posterior subcapsular cataract.

For practice, the time of occurrence of the listed undesirable effects, as well as their dependence on the dose and some other factors, are very important (Table 23.4).

**Table 23.4. Time and conditions for the occurrence of undesirable effects of GCS**

| | |
|---|---|
| At the start of treatment (usually is impossible to avoid) | Sleep disorders<br>Emotional lability<br>Increased appetite<br>Weight gain |
| In patients at risk groups and with concomitant usage of other drugs | Arterial hypertension<br>Hyperglycemia (up to the development of diabetes)<br>Ulcerogenic effect<br>Acne |
| With supportive or intensive care (risk decreases with use minimum doses and sparing modes) | Cushingoid syndrome<br>Inhibition of the hypothalamic-pituitary- adrenal system<br>Infectious complications<br>Osteonecrosis<br>Myopathy<br>Impaired wound healing |
| Late reactions (possibly dose dependent) | Osteoporosis<br>Skin atrophy<br>Cataract<br>Atherosclerosis<br>Growth retardation<br>Fatty degeneration of the liver |
| Rare and unpredictable complications | Psychosis<br>Glaucoma<br>Hypertension-hydrocephalic syndrome<br>Epidural lipomatosis<br>Pancreatitis |

**Drug interactions**.

The effect of corticosteroids is enhanced by the concomitant administration of erythromycin (slows down the metabolism of corticosteroids in the liver), salicylates (increases the non-protein fraction of corticosteroids), estrogens.

The effect of corticosteroids is weakened by inducers of microsomal liver enzymes - phenobarbital, phenytoin, rifampicin, etc.

GCS weaken the effect of anticoagulants, antidiabetic and antihypertensive drugs.

GCS enhance the action (including undesirable effects) of theophylline, adrenomimetics, immunosuppressants, NSAIDs.

**Contraindications**

Distinguish between absolute and relative.

*Absolute*

~ Individual intolerance to the drug

In short-term treatment with high doses of corticosteroids for health reasons there are no contraindications. When planning long-term therapy, relative contraindications must be taken into account.

*Relative*:

~ Generalized mycosis, herpetic infection, active form of tuberculosis.
~ Peptic ulcer, diverticulitis, newly created intestinal anastomosis.
~ Diabetes.
~ Obesity III–IV type.
~ Severe arterial hypertension.
~ Mental illness, epilepsy.
~ Severe osteoporosis.
~ Myasthenia.
~ Renal failure.

For intra-articular injection, contraindications are: infectious lesions of the joint and periarticular soft tissues, previous arthroplasty, intra-articular fracture, pathologically mobile joint, blood clotting disorders.

**Clinical features of the use of GCS.**

*Use during pregnancy and lactation*. The systemic use of any GCS and the local use of triamcinolone and fluocinolone are considered contraindicated during pregnancy (especially in the first trimester) and during breastfeeding. However, in each case, it is necessary to evaluate the ratio of the expected benefit to the mother and the possible harm to the fetus. Topical application in these cases requires special care.

**Types (forms) of GCS therapy**:

~ replacement therapy - in case of insufficiency of the adrenal cortex of any etiology; GCS is prescribed in doses close to the daily physiological

secretion of hydrocortisone - physiological doses (20–30 mg of hydrocortisone or 5–7.5 mg of prednisolone);

- ~ suppressive (blocking, suppressive) therapy - with adrenogenital syndrome; GCS is prescribed in doses exceeding physiological - pharmacological doses, which leads to suppression of ACTH secretion and a subsequent decrease in androgen hypersecretion by the adrenal cortex;
- ~ pharmacodynamic therapy - the most common use of corticosteroids;
- ~ it is divided into systemic - inside, intravenously, intramuscularly and local -inhalation (topical forms of corticosteroids), intra- and periarticular, intradermal,
- ~ application (on the skin and mucous membranes), epidurally, in the cavity, etc.; the division into systemic and local therapy is rather arbitrary, since the absorption of GCS in some cases of topical application may be so great that systemic undesirable effects develop.

**Use in dentistry.**

1. *Most mucosal lesions of non-microbial etiology respond* well to local treatment with corticosteroids (triamcinolone, hydrocortisone, betamethasone). The maximum effect is observed with prolonged direct contact of GCS with the affected area. For severe ulceration SOPR it is expedient to prescribe systemic corticosteroids (prednisolone, etc.) In some cases, the preferred option is the injection of corticosteroids into the affected area (triamcinolone, hydrocortisone).
   In case of infectious lesions of the oral mucosa (for example, herpes), the use of HA is unacceptable.

2. *With aphthous stomatitis*, the effectiveness of GCS is currently considered proven. In this case, topical triamcinolone is more commonly used.

3. *Treatment of arthritis* of the temporomandibular joint GCS can be carried out both systemically and locally. In the case of monoarthritis, intraarticular administration of betamethasone or triamcinolone is indicated, which relieves pain, relieves inflammation and improves motor activity.

4. *In pulpitis*, the possibility of topical application of triamcinolone (together with tetracycline) is being studied.

5. *The use of corticosteroids in some emergency conditions* - see the relevant sections of Ch. 30.

**Tactics of managing dental patients receiving or previously treated GCS**.

Patients taking corticosteroids usually do not need dose adjustment if they have dental procedures. The exception is persons experiencing a strong fear of dental procedures, and undergoing major surgical interventions. In these cases, there is a need for an additional appointment of GCS (Table 23.5).

**Table 23.5. Principles of management of dental patients taking or taking GCs**

| | |
|---|---|
| Purpose of appointment or increase doses of corticosteroids | prevention of development of acute insufficiency of the cortex adrenal glands under stress |
| Stress prevention and timely diagnosis adaptation disorders is achieved by | optimal anesthesia<br>postoperative pain relief<br>blood pressure control |
| Additional prescribtion of the GCS is not required for: | cancellation of GCS more than 1 year ago,<br>daily dose of hydrocortisone <20 mg or >40 mg, (prednisolone or mazipredone <5 mg or >10 mg,<br>local therapy - ointments and creams for skin rashes,<br>metered dose inhalers for asthma,<br>nasal spray |
| Additional prescription of GCS is not required for: | at a dose of hydrocortisone 20–40 mg / day (prednisolone or mazipredone) 5–10 mg/day,<br>topical therapy (see above) at very high doses or all over the body |
| Additional prescribtion of GCS (depend on stressfulness of the intervention and severity of pain) | A) on the day of the dental intervention doubling the morning dose used<br>B) the day before, on the day, and within 2 days after intervention, the dose used is doubled |

**Drugs**

*Hydrocortisone* - natural GCS, 4 times inferior in GCS activity to prednisolone; mineralocorticoid activity is somewhat superior to it. It has a significant effect on water-electrolyte metabolism (there is a high probability of developing edema, sodium retention and potassium loss). Hydrocortisone hemisuccinate and sodium succinate are used for the preparation of solutions, administered intravenously, have a fast and relatively short duration of action. Hydrocortisone acetate is used to prepare a microcrystalline suspension, which is injected into cavities and tissues; its effect develops slowly and lasts for a long time.

Available in tablets of 5, 10 and 20 mg; in the form of a lyophilized powder for solution for injection or as a solution for injection in ampoules and vials of 25, 100 and 500 mg; in the form of a microcrystalline suspension in ampoules and vials of 5 ml of 25 mg / ml, as well as in the form of 1% cream and 1% ointment in tubes.

*Prednisolone or mazipredone* (prednisol, decortin H5, decortin H20, decortin H50, medopred, prednisolone, prednisolone acetate, prednisolone hemisuccinate,) is a synthetic non-fluorinated corticosteroid, the most commonly used in clinical practice due to a relatively good ratio of efficacy, safety and economy.

*Mazipredone* is a derivative of prednisolone, which practically does not differ from prednisolone in its pharmacological properties and is sold under the commercial name "prednisolone".

Available in tablets of 1.5, 5, 10, 20 and 50 mg; as a solution for injection in ampoules of 30 mg; in the form of a powder for solution for injections of 10, 25, 50 and 250 mg; in the form of a suspension for injections of 10, 20, 25 and 50 mg; in the form of 0.25 and 0.5% ointment in tubes.

*Triamcinolone* (azmacort, berlikort, kenalog, kenalog 40, kenalog orabase, polcortolone, polkortolone 40, triacort, triamcinolone, triamcinolone, fluorocort) - fluorinated GCS, which has a stronger and more lasting effect thanprednisolone; has practically no mineralocorticoid activity; more often causes undesirable effects, especially myopathy, striae, hemorrhages, hirsutism.

Available in tablets of 2, 4 and 8 mg; in the form of a metered aerosol in vials 240 doses, 100 mcg/dose; in the form of a suspension for injection in ampoules and vials of 1 and 5 ml of 10 and 40 mg/ml; in the form of a solution for injection in ampoules of 1 ml of 40 mg; as a 0.1% oral paste; in the form of 0.1% cream in tubes and 0.025% 0.1% ointment in tubes and dark glass jars.

*Betamethasone* (Acriderm, Beloderm, Diprolene, Diprospan, Celestoderm B, Celeston) - fluorinated GCS is 8-10 times more active than prednisolone; practically has

no mineralocorticoid properties; it is not recommended to prescribe for a long time due to the strong inhibition of the hypothalamic-pituitary-adrenal system.

Available in tablets of 0.5 mg; in the form of a solution for injection in ampoules of 1 ml of 4 mg; in the form of a solution and suspension for injection in ampoules of 2 mg of betamethasone disodium phosphate and 5 mg of betamethasone dipropionate; in the form of 0.064% cream, 0.05% and 0.1% cream or ointment in tubes.

*Dexamethasone* (dexazone, dexamethasone, dexone, fortecortin, fortecortin mono) - fluorinated GCS is 7-8 times more active than prednisolone; practically does not have a mineralocorticoid effect; it is not recommended to prescribe for a long time due to the strong inhibition of the hypothalamic-pituitary-adrenal system.

The drug has a decongestant effect, it is credited with the ability to reduce cerebral edema. In connection with this and some other properties, bacterial meningitis, cerebral edema, prevention treatment of nausea and vomiting during chemotherapy, treatment of severe withdrawal syndrome in alcoholism, prevention of respiratory distress syndrome in preterm infants.

Available in tablets of 0.5, 1.5 and 4 mg and as a solution for injection in ampoules iflacons 4, 8 and 40 mg.

## Control questions

1. What is not an indication for the appointment of GCS in dentistry?

a) Desquamative gingivitis.
b) Aphthous stomatitis.
c) Herpetic lesions of the oral mucosa.
d) Arthritis of the temporomandibular joint.
e) Pemphigus.

2. Which of the following drugs belongs to fluorinated corticosteroids?

a) Cortisone.
b) Methylprednisolone.
c) Hydrocortisone.
d) Triamcinolone.
e) Prednisolone.

3. Which of the following drugs, when used systemically, has the least duration of action?

a) Hydrocortisone.
b) Prednisolone.
c) Methylprednisolone.
d) Triamcinolone.
e) Betamethasone.

4. Which of the following phenomena is not related to pharmacodynamic effects GCS?

a) Slowing down the excretion of sodium and water from the body.
b) Stimulation of gluconeogenesis in the liver.
c) Increased absorption of calcium in the intestine.
d) Inhibition of all phases of inflammation.
e) Stimulation of the formation of red blood cells.

5. Which of the types of therapy cannot be carried out with the help of corticosteroids?

a) Replacement therapy.
b) Etiotropic therapy.
c) Suppressive therapy.
d) Pharmacodynamic therapy.
e) Any type of therapy can be carried out.

6. Which of the following undesirable effects can cause corticosteroids?

a) Atrioventricular heart block.
b) Arterial hypotension.
c) Bronchial obstruction.
d) Arterial hypertension.
e) Ischemic heart disease.

7. The effect of GCS is enhanced with concomitant administration:

a) Rifampicin.
b) Erythromycin.
c) Phenobarbital.
d) Difenina.
e) Ampicillin.

8. The clinical effect of which drugs weaken GCS?

a) NSAIDs.
b) Anticoagulants.
c) Sympathomimetics.
d) Immunosuppressants.
e) Antihistamines.

9. Relative contraindications to the appointment of HA do not include:

a) Diabetes mellitus.
b) Peptic ulcer of the stomach.
c) Severe osteoporosis.
d) Severe arterial hypertension.
e) Long-term rheumatoid arthritis.

10. In what cases do dental patients receiving corticosteroids need an increase in their doses?

a) In the presence of severe cardiovascular pathology.
b) In cases of anamnestic indications of allergic reactions to local anesthetics in history.
c) In cases where these patients have a strong fear of dental procedures.
d) In the presence of diabetes mellitus, for which the patient receives insulin.
e) With severe osteoporosis.

# Chapter 24 Immunocorrectors.

*Immunomodulators* (immunocorrectors) are substances that have a multidirectional effect on the immune system, depending on its initial state(increase low and lower high levels of immune status) (R.M. Khaitov).

Immunomodulators are used in the complex therapy of diseases, accompanied by clinical signs of secondary immune deficiency, which is characterized by frequently recurrent, chronic infections.

**Indications for use in dentistry**

In dentistry, immunomodulators are used in the treatment of chronic, recurrent diseases of the oral mucosa and periodontium, glossitis, chronic infectious and inflammatory diseases of the maxillofacial region, for the profileClinics and treatment of postoperative infectious complications after tooth extraction, implantation of artificial dental roots.

Table 24.1. oral protective factors.

**Local immunity**

A. Cell membranes of the oral mucosa
B. Saliva
    - polymorphonuclear neutrophils
    - enzymes involved in the local mechanism of cell lysis and protection (lysozyme, acid phosphatase, esterase, etc.)
    - lactoferrin (a protein that binds iron and makes it unavailable for bacterial metabolism)
    - secretory immunoglobulin A (sIgA)
C. Gingival fluid
    - polymorphonuclear neutrophils
    - lactoferrin

**General immunity**

A. Non-specific immune responses
    - polymorphonuclear neutrophils and macrophages
    - mediators of the inflammatory reaction, chemotaxis and redox reactions produced by macrophages and polymorphonuclear neutrophils

- interferon Y (required for the interaction of immunocompetent cells),interleukin-2 (increases the secretion of immunoglobulins by B-lymphocytes and enhances local cellular defense reactions) produced by CD4 (T-lymphocytes (helpers)

B. Specific immunity
- oral lymphoid tissue (sIgA synthesis)
- cellular elements of specific mucosal immunity
- T - lymphocytes (depending on the specialization, they enhance the local immune response to the appearance of a foreign antigen or destroy it)
- plasma cells, B-lymphocytes (synthesis and secretion of immunoglobulins)
- specific humoral immunity - immunoglobulins G, M, A enter the site of immune conflict from the blood or are synthesized in the oral cavity by plasma cells after specific stimulation

**Table 24.2. Classification of immunomodulators**.

1. Exogenous origin - products of microorganisms (bacterial vaccines):
   - systemic action (broncho-munal, ribomunil)
   - local action (IRS-19, imudon)
2. Endogenous origin:

A. Extracts of thymus immunoregulatory peptides
   - natural (thymalin, taktivin, myelopid, timaktid)
   - synthesized (thymogen)

B. Cytokines (interleukins, interferons, etc.)

3. Chemically pure and synthesized substances
   - well-known drugs with immunomodulatory properties (levamisole, methyluracil, sodium nucleinate, dibazol)
   - obtained by targeted chemical synthesis (polyoxidonium)
   - analogues of immunomodulators of endogenous origin (licopid, imunofan)
4. Immunoglobulins

**Immunomodulators of exogenous origin**.

Bacterial vaccines contain ribosomal fractions and proteoglycans of the membrane part of the bacterial cell or lyophilized lysates of bacteria that are the most common causative agents of respiratory infections (bronchomunal, ribomunil, IRS-19) or oral cavity (imudon).

**Table 24.3 Composition of bacterial vaccines**.

| Broncho - munal | Ribomunil | IRS - 19 | Imudon |
|---|---|---|---|
| S. pneumoniae<br>H. influenzae<br>K. pneumoniae<br>K. ozaenae<br>S. aureus<br>S. viridans<br>S. pyogenes<br>Moraxella catarrhalis | K. pneumoniae<br>S. pneumoniae<br>S. pyogenes<br>H. influenzae | S. pneumoniae (6)<br>H. influenzae type B<br>K. pneumoniae<br>S. aureus,<br>Acinetobacter calcoaceticus baumanni variety<br>Moraxella catarrhalis<br>Neisseria subflava flava variety<br>Neisseria subflava perflava variety<br>S. pyogenes group. A<br>S. dysgalactiae group C,<br>Enterococcus faecalis<br>Enterococcus faecalis,<br>Streptococcus group G | Lactobacillus acidophilus,<br>L. helveticus,<br>L. lactis,<br>L. fermentatum,<br>S. pyogenes (2),<br>S. faecium,<br>S. faecalis,<br>S. sanguis,<br>S. aureus,<br>K. pneumoniae,<br>Corynebacterium pseudodiphtheriae,<br>Fusobacterium fusiforme,<br>Candida albicans |

**Mechanism of action, pharmacodynamic effects**.

They combine the properties of a bacterial vaccine and a nonspecific immunocorrector.

Their use stimulates cellular and humoral immunity, activates nonspecific defense factors.

Systemic drugs (bronchomunal, ribomunil) increase the formation of specific antibodies to pathogens, phagocytic activity, stimulate the functions of T- and B-lymphocytes, the production of serum and secretory immunoglobulins, interleukins, alpha-interferon.

Local drugs (IRS-19, imudon) affect the state of local immunity, stimulating the production of sIgA, phagocytosis, and increase the content of lysozyme in saliva. Imudon inhibits the oxidative metabolism of polymorphonuclear leukocytes in saliva and gingival fluid, reducing the damaging effect of free radicals on the cells of the oral mucosa. Their use increases the secretion of immunoregulatory cytokines, in particular alpha-interferon, interleukin-2.

*The indication* for their appointment is the prevention and treatment of respiratory infections (broncho-munal, ribomunil, IRS-19) and the oral cavity (imudon).

*Contraindications* - hypersensitivity reactions. Systemic drugs (broncho-munal, ribomunil) are not using in pregnant and lactating women.

With caution, bacterial vaccines are using in patients with systemic, autoimmune diseases, HIV infection.

*Drug interactions* - possible combined use with antibacterial, antiviral and antifungal drugs. There should be a break of 4 weeks between taking oral vaccines and broncho-munal.

*Undesirable effects*:

- ~ allergy
- ~ hypersalivation (ribomunil)
- ~ increased T body, abdominal pain, nausea, vomiting, diarrhea (broncho-munal)
- ~ sneezing, nasal discharge (ITS-19)

**Drugs of endogenous origin**

*Immunoregulatory peptides* are complexes of polypeptide fractions, isolated from the thymus gland of cattle or obtained synthetically. They influence differentiation and stimulate T-lymphocytes. Treatment with these drugs should be carried out under the control of the parameters of the immune system.

*Indications for use*:

- ~ replacement therapy for primary and secondary deficiency of thymic hormones.
- ~ secondary immunodeficiency states, accompanied by recurrent bacterial and fungal infections of various localization

*Contraindications*:

- ~ hypersensitivity
- ~ pregnancy with the presence of Rh-conflict (tactivin, thymalin, myelopid)
- ~ bronchial asthma (tactivin)
- ~ simultaneous administration of two drugs of this group

*Unwanted effects:*

- ~ allergic reactions
- ~ exacerbation of purulent infections (tactivin).

*Cytokines*. Cytokines are an extensive family of biologically active peptides that ensure the interaction of cells of the immune, hematopoietic, nervous, endocrine systems. Cytokines are mediators of immune and inflammatory responses. The main

classes of cytokines include interleukins, interferons, colony stimulating factors, tumor necrosis factors and the family of transforming growth factors. Cytokines are included in complex therapy for the correction of immunodeficiency states in infectious diseases, stimulation of antitumor immunity, prevention of complications during radiation and chemotherapy, transplantation of organs and tissues. Treatment with cytokines is carried out under the control of immune indicators, including cytokine status. The clinical efficacy of cytokines and their place in the treatment of various diseases needs further study.

**Chemically pure and synthesized substances**.

These drugs affect the activation and proliferation of T-lymphocytes, macrophages, production of immunoglobulins, interferon.

The effectiveness of methyluracil, dibazol, sodium nucleinate has not been proven and their routine use is not justified.

Levamisole causes leukopenia, respiratory arrest, pulmonary hypertension, proteinuria. Given its toxicity, it is recommended by the WHO for use only in patients with stage 1V colon cancer. In a short course, it is used as an antihelminthic.

Polyoxidonium, imunofan, licopid are used for secondary immunodeficiencies in patients with infectious, oncological diseases.

Contraindication to their appointment is pregnancy, hypersensitivity reactions. Against the background of their use, the development of allergic reactions is possible, temperature increase (licopid).

**Immunoglobulins.**

Obtained from the plasma of healthy people tested for the presence of antibodies to HIV, hepatitis C virus, HbsAg.

They contain antibodies of different specificity, have a non-specific immunomodulatory effect.

They *are used* for urgent prevention and treatment of infectious, infectious-inflammatory diseases, treatment of hypo- and agammaglobulinemia.

*Contraindications* for their appointment are allergic reactions to the introduction of blood products.

*With caution* should be used in patients with systemic immune diseases. Immunoglobulins for intramuscular administration are forbidden to be administered intravenously. After the end of the administration of the drug, it is necessary to monitor the patient's condition for at least 30 minutes.

*Undesirable effects* - hyperemia of the skin at the injection site, fever, chills, rarely allergic reactions.

If immunoglobulin was administered to the patient in the first two weeks after vaccination against measles, rubella, mumps, then the vaccination should be repeated, but not earlier than after 3 months after i / m and 6 months. after intravenous administration of immunoglobulin.

**Drugs**

*Imudon* is a mixture of lysates of the most common infectious agents in dentistry(composition see above). It reduces inflammation, pain, bleeding of the oral mucosa, halitosis, faster epithelization of erosions and ulcers. Imudon does not have a systemic effect.

*Indications for use* - periodontal disease, periodontitis, gingivitis, stomatitis, glossitis, mucosal damage caused by dentures, prevention and treatment of infectious complications during extraction and implantation of teeth, pharyngitis, prevention and treatment of infectious complications during tonsillectomy.

*Contraindications* - hypersensitivity.

There are no data on *the adverse effects* of imudon when used in pregnant women. 1 tablet of imudon contains 15 mg of sodium, which should be taken into account when prescribing drug in patients with circulatory failure and arterial hypertension.

No data on unwanted drugs interactions of imudon. May be combined use with antibacterial, antiviral and antifungal drugs.

*Undesirable effects* - in rare cases, nausea and discomfort in epigastrium.

Release form - lozenges. In acute and exacerbation of chronic inflammatory diseases of the oral cavity are prescribed for adults and children over 14 years old 8 tab. per day, children from 1 to 14 years old - 6 tab. The average course duration is 10 days.

For the prevention of exacerbations of chronic inflammatory diseases of the oral cavity - adults and children over 1 year old - 6 tablets per day for 20 days or more (interval between doses 3 - 4 hours). It is recommended to carry out 2 - 3 courses of treatment per year.

For the prevention and treatment of postoperative complications - 8 tab. per day for 1 week before surgery and 8-10 tablets per day for a week after surgery.

Rinse your mouth and eat food no earlier than an hour after taking drug.

## Control questions

1. In a patient with mild chronic generalized periodontitis, purpose:

a) antistaphylococcal immunoglobulin
b) IRS-19
c) ribomunil
d) imudon
e) levamisole

2. Undesirable effects of levamisole:

a) leukopenia
b) pulmonary hypertension
c) respiratory arrest
d) nausea, vomiting
e) all of the above

3. Correct regarding imudon:

a) increases the content of sIgA
b) increases the content of IgG in the blood
c) when it is used, the activity of blood enzymes increases
d) all of the above is correct
e) all of the above is incorrect

4. Specify an immunomodulator from the group of bacterial vaccines:

a) polyoxidonium
b) thymalin
c) imudon
d) methyluracil
e) immunoglobulin

5. Wrong about imudon:

a) increases the content of lysozyme in saliva
b) increases the activity of phagocytes
c) is used to prevent ARI
d) destroys bad breath
e) inhibits the oxidative metabolism of polymorphonuclear neutrophils

# Chapter 25 Drugs affecting hemostasis.

Drugs that affect hemostasis are drugs that prevent the formation of a blood clot or act on an already formed blood clot, and drugs that accelerate coagulation (antihemorrhagic drugs).

Hemostasis is a physiological process that occurs in four stage:

- ~ local vasoconstriction;
- ~ adhesion and aggregation of platelets to form platelet ("white") blood clot;
- ~ activation of the blood coagulation system with the formation of fibrin and the formation of a "red" thrombus;
- ~ fibrinolysis (thrombolysis).

There is a physiological balance between the coagulation and anticoagulation systems of the blood. In the presence of risk factors, conditions are created for pathological thrombosis, thromboembolism (Table 25.1) and the occurrence of bleeding and bleeding (Table 25.2).

**Table 25.1. Risk factors for thrombosis and thromboembolism**

| | |
|---|---|
| Arterial thromboses | violation of lipid metabolism and obesity;<br>ischemic heart disease;<br>hypertonic disease;<br>diabetes;<br>smoking;<br>psychogenic shock |
| Venous thrombosis and thromboembolism | hypodynamia<br>oncopathology;<br>surgical interventions and trauma;<br>pregnancy and childbirth;<br>acute blood loss;<br>drug therapy and invasive treatments;<br>oral contraceptives;<br>allergic reactions |

Bleeding can develop against the background of drug therapy or pathological processes, at the level of platelets, the vascular wall or coagulation factors, trauma,

operations, tooth extraction, as well as diseases accompanied by erosion or rupture of the vascular wall.

**Table 25.2. Risk factors for bleeding and bleeding**

| | |
|---|---|
| Platelets | thrombocytopenia;<br>platelet aggregation disorders, including those caused by drugs |
| Vascular wall | increased permeability |
| System coagulation | congenital deficiency of blood clotting factors (hemophilia and others);<br>anticoagulant therapy |

Thrombocytopenia (normal platelet count 150,000–400,000 in μl-1) - a decrease in the number of platelets of 150,000 per μl-1, can be observed with radiation therapy, connective tissue diseases, leukemia, as a side effect of heparin. With a decrease in the platelet count of 50,000 in μl-1, platelet transfusion is necessary before dental operations. Thrombocytopenia in idiopathic thrombocytopenic purpura (Werlhof's disease) requires the appointment of glucocorticoids. Platelet aggregation is impaired by the use of antiplatelet agents, NSAIDs, sodium valproate and a number of other drugs.

An increase in the permeability of the vascular wall is observed with a deficiency of vitamin C, long-term glucocorticoid therapy. In these cases, suturing provides adequate hemostasis for bleeding associated with dental procedures.

Coagulation factor deficiency seen in congenital diseases(hemophilia - deficiency of factor VIII; congenital deficiency of factor IX, von Willebrand factor) or with an overdose of heparin or indirect anticoagulants. In this case, the most reliable method of treatment is the introduction of clotting factors.

## 25.1 Anticoagulants, fibrinolytics, antiplatelet agents

*Anticoagulants* are drugs that inhibit the biological activity of the main plasma factors of the coagulation system or their synthesis.

**Classification**

All anticoagulants are divided into two main groups:

- Direct anticoagulants: unfractionated heparin and low molecular weight heparin (nadroparin, enoxaparin, etc.)
- Indirect anticoagulants (warfarin, etc.)

**Indications for use in dentistry:**

- prevention and treatment of thrombosis of the facial veins and cavernous sinus;
- prevention of thrombosis and thromboembolism if the patient has risk factors;

~ emergency conditions - acute coronary syndrome, thromboembolism of the pulmonary artery and peripheral veins.

**Direct anticoagulants**

This group includes unfractionated heparin (UFH) and low molecular weight heparins (LMWH). Heparin is a naturally occurring mucopolysaccharide compound found in mast cells. The molecular weight of natural heparin ranges from 4,000 to 40,000. By fractionation, LMWHs are obtained from natural UFH, which have a molecular weight of about 5000. Their representatives are enoxaparin, dalteparin, nadroparin and other drugs.

LMWHs have the following advantages over UFH:

~ more predictable anticoagulant effect;
~ higher bioavailability when administered subcutaneously;
~ longer action and less frequency of administration;
~ possibility of use without laboratory control;
~ hemorrhagic complications and thrombocytopenia are observed much less frequently;
~ more convenient to use, as they are available in syringes in fixed doses.

LMWHs are gradually replacing UFHs as their higher cost is offset by better tolerability, ease of use, and no need for laboratory monitoring.

**Mechanism of action**

The action of UFH is based on the ability to activate antithrombin III, which inhibits plasma coagulation factors such as thrombin (factor II), factor IXa, factor Xa, etc. Antithrombin III in the presence of heparin is activated more than 1000 times, which causes hypocoagulation. LMWHs bind only to factor Xa and practically do not inhibit blood coagulation at the level of thrombin (Fig. 4).

**Main clinical effect**: anticoagulant.

**Pharmacokinetics**

*Absorption*. All types of heparin are administered intravenously or subcutaneously, because. when taken orally, heparin is destroyed. Due to the unpredictability of pharmacokinetics and therefore effect, heparins should not be administered intramuscularly. Topical application in the form of creams, gels is moderately effective only with damage to the superficial veins.

*Bioavailability*. When administered subcutaneously, the bioavailability of UFH is 20%, LMWH - 80%. With intravenous administration, the effect occurs immediately. The maximum effect develops after 5-10 minutes and lasts up to 4 hours. T1 / 2 UFG is 1-5 hours and depends on the dose. LMWH have T1 / 2 - 3-4 hours, in elderly patients and with renal failure increases to 6-7 hours.

*Distribution in the body*. Heparins do not cross the placental barrier and are not excreted in breast milk.

*Metabolism and elimination*. Heparins are metabolized by heparinase excreted by the kidneys. With subcutaneous administration, the frequency of administration of UFH is 2 times a day. LMWHs are eliminated more slowly, so it is possible to administer them once a day.

**Laboratory monitoring of the effectiveness and safety of heparin**

When using UFH in therapeutic doses to control the level of hypocoagulation, the main test is **activated partial thromboplastin APTT time** . An increase in APTT by 2.0-2.5 times corresponds to therapeutic hypocoagulation. An increase in APTT> 3.0–3.5 times is fraught with the risk of bleeding. With intravenous infusion of therapeutic doses, the determination of APTT is carried out every 4-6 hours, and with subcutaneous administration - 6 hours after the injection. If there is a risk of bleeding (an increase in APTT> 3.0–3.5 times), heparin administration is suspended, the dose is reduced. With the development of bleeding, an antagonist of protamine sulfate is used.

An outdated control method is the determination of blood clotting time.

It is also not justified to perform the so-called coagulogram, especially in patients who do not have diseases of the blood coagulation system.

The appointment of prophylactic doses of UFH, any doses of LMWH does not require monitoring of APTT.

**Adverse reactions**

Bleeding (Table 25.3) of varying severity (hematomas at injection sites, bleeding from peptic ulcers, kidneys, into joints, from an operating wound, from the hole after tooth extraction) can be observed in 5-10% of patients using UFH and 2-3 times less often against the background of LMWH use.

Risk factors for bleeding when prescribing direct anticoagulants:

- fresh surgical incision;
- trauma;
- tooth extraction;
- thrombocytopenia;
- alcohol abuse (the risk increases by 7 times);

~ age 60 years (the risk increases by 3 times);
~ urea level 8.3 mmol/l (the risk increases by 1.5 times);
~ women (the risk increases by 2 times)

*Thrombocytopenia* ( 150,000 in µl-1):

a) *reversible* (transient, early), characterized by the formation of platelet aggregates in the first 3-5 days of treatment and does not need to be corrected;

b) *irreversible* (immune, late) can be observed on days 5-10 of therapy in the "white blood clot" syndrome (in 0.2% of cases) and even DIC. white blood clot syndrome represents localized platelet aggregation against the background of systemic thrombocytopenia and is accompanied by ischemia, infarction, gangrene with a mortality rate of up to 25%. Limiting the duration of the course of heparin therapy can reduce the risk of developing thrombocytopenia. Treatment consists in the abolition of heparin and the use of direct thrombin inhibitors (hirudin, argatroban).

**Allergic and anaphylactic reactions.**

*Skin*: the formation of painful nodules at the sites of subcutaneous injection; with prolonged use of UFH, dysostia (burning, itching) in the area of \u200b\u200bthe soles, reversible alopecia areata.

*Musculoskeletal system*: osteoporosis.

*Immune system*: decrease in the level of T and B-lymphocytes.

*Withdrawal syndrome* ("reactivation"): thrombus formation after discontinuation of heparin in patients with unstable angina.

**Drug Interactions**

*The hypocoagulative effect* of heparin increases when combined with dextrans, ergot alkaloids, ASA, NSAIDs, dipyridamole. The weakening of the effect of heparin is possible as a result of inactivation when introduced into one syringe with glucose, aminoglycosides and erythromycin.

*Clinical features of the application* NFG prescription given to patients in a hospital setting. In order to prevent thrombosis and thromboembolism, 10,000-15,000 IU / day is used in 2-3 doses subcutaneously or in 4-6 intravenous injections. Subcutaneous injection is carried out through a thin short needle perpendicular to the skin fold in the iliac and subclavian region.

*Therapeutic doses* range from 20,000-60,000 IU / day. They are administered by intravenous infusion, bolus (4-6 times a day) or subcutaneously. Infusion begins with a jet injection of 5000 IU, then 30 IU / kg / h. When using therapeutic doses, infusion of

the drug is preferable, since hypo- and hypercoagulability drops are possible with bolus administration.

The duration of the course is usually 5-7 days. If a longer reduction in blood coagulability is required, an indirect anticoagulant, most often warfarin, is prescribed 2-3 days before heparin is discontinued. In order to avoid the "rebound" syndrome, high doses of UFH are reduced gradually.

For the prevention of thromboembolism in the postoperative period, UFH and LMWH are administered to patients at risk 2 hours before (!) surgery and stopped at the end of bed rest. The introduction of low doses of heparin before surgery is due to the fact that thrombus formation in deep veins begins during surgery.

*Contraindications* to the prescription of direct anticoagulants:

*Absolute*

- early postoperative period (during operations on the brain, eyes, prostate);
- endocarditis;
- damage to the brain and spinal cord;
- local and spinal anesthesia;
- severe renal and hepatic insufficiency;
- uncontrolled arterial hypertension;
- hemorrhagic stroke.

*Relative*

- peptic ulcer of the stomach and duodenum

**Tactics of managing dental patients receiving heparin drugs**

If necessary, an emergency dental procedure is performed when minimal severity of hypocoagulation - 4-6 hours after intravenous administration one dose of heparin. If heparin infusion is continued, intravenous protamine sulfate is recommended at a rate of 1 mg per 100 IU of heparin. APTT is monitored. With the development of bleeding, local hemostasis is sufficient.

**Drugs**

*Heparin* is available in the form of sodium and calcium salts. 5 ml vials contain 5000 or 25000 IU in 1 ml.

*Enoxaparin* (Clexane, Lovenox) with a moderate risk of developing thrombosis, it is administered at a dose of 20 mg (2500 IU), with a high risk - 40 mg, coronary syndrome - 80 mg. Available in syringes of 20-100 mg (0.2-1ml).

*Nadroparin* (fraxiparin). For the prevention of postoperative thrombosis, 0.2-0.4 ml is administered before surgery and 0.3-0.6 ml in the postoperative period in accordance with the patient's weight (50-95 kg). For the treatment of venous thrombosis, doses of 0.5-1.0 ml are administered 2 times a day (with a patient weighing 55-90 kg). Produced in the form of a disposable syringe - ampoules, contains a dose of 0.3-1 ml (2850-9500 anti Ha).

**Indirect anticoagulants**

The group of indirect anticoagulants includes coumarin derivatives (warfarin, etc.) and indandione derivatives (phenindione, etc.). Currently, warfarin is the main drug, as it causes less allergic reactions and has a more predictable anticoagulant effect. Unlike heparin, indirect anticoagulants have no effect in vitro, this determines the name "indirect". All drugs are used orally.

**Mechanism of action**

Indirect anticoagulants inhibit the vitamin K cycle, participating in the synthesis of various blood coagulation factors (II, YII, IX, X, etc.), therefore they are also called vitamin K antagonists.

**Main clinical effect**: anticoagulant.

**Pharmacokinetics**

Warfarin is absorbed rapidly and completely. The maximum plasma concentration is created after 12-36 hours. The effect develops gradually after 8-12 hours after administration and persists for 2-5 days after discontinuation of the drug. Warfarin is 97-99% bound to plasma proteins and is easily displaced from this compound by other drugs. Metabolism is carried out in the liver.

Laboratory monitoring of the effectiveness and safety of indirect anticoagulants To monitor the effectiveness and safety of indirect anticoagulants earlier used prothrombin time (PT), which is measured in seconds; prothrombin index (PI), which is measured in% and is normally 80-110%. Currently, the international normalized ratio is the standard control method, which is normally 0.7-1.1. *Definitions of other options clotting system is not required.*

Studies are carried out before prescribing the drug, on the 3rd day of admission, then every other day for a week and, in the future, once a month with stable indicators.

*Efficiency criterion* (therapeutic hypocoagulation): increase in INR by 2-2.5 times. During dental procedures, the risk of bleeding occurs with INR>3.

**Adverse reactions**

*Oral cavity*: bleeding from the gums, hemorrhages on the hard palate and mucosa, stomatitis, pain, inflammation of the salivary glands, ecchymosis on the mucosa.

*Bleeding andbleeding*: epistaxis, hematuria, menorrhagia, intracranial hemorrhage. With hypocoagulation in excess of therapeutic, it is necessary to cancel the drug, introduce active vitamin K1 - phytomenadione at a dose of 10-50 mg intravenously. With the development of bleeding, along with the introduction of vitamin K preparations, it is necessary to introduce fresh frozen plasma, cryoglobulin or another concentrate of clotting factors.

*Hematological effects:* "ricochet" thrombosis, agranulocytosis.

*Allergic reactions*: Quincke's edema (most typical for indandione derivatives).

*Skin*: patchy and vesicular skin lesions, skin necrosis in the facial area, ear shells.

*Special reactions*: purple fingers syndrome in the form of purple erythema of the feet and thumbs.

*Teratogenic action*.

**Drug Interactions**

A feature of indirect anticoagulants is the great dependence of their effect on many factors: gender, diet, concomitant diseases and concomitant drug therapy. More than 250 drugs, including vegetable (St. John's wort, ginkgo biloba, etc.) can interact with them.

*Strengthening the effect of indirect anticoagulants* is observed against the background of the use of inhibitors of microsomal liver enzymes (co-trimoxazole, metronidazole, etc.); drugs, displacing anticoagulants from the connection with proteins (salicylates, etc.); suppressing intestinal microflora (antibiotics); drugs that reduce the absorption of vitamin K in the intestine (cytostatics); anabolic hormones; alcohol; antiplatelet agents and even cranberry juice.

Inducers of microsomal liver enzymes contribute to a decrease in the effect(barbiturates, rifampicin, etc.); activated charcoal, antacids (impaired absorption);diuretics (especially in patients with heart failure); oral contraceptives.

Indirect anticoagulants themselves can enhance the effect of hypoglycemic drugs, carbamazepine and weaken the effect of oral contraceptives.

The effect of indirect anticoagulants is enhanced by hypoalbuminemia, vitamin K deficiency, alcoholism, and liver diseases.

INR control is a measure to prevent bleeding in unidentified drug interactions of warfarin, including those with herbal remedies.

Indirect anticoagulants are prescribed for both developed thrombosis, in order to limit their further growth, and for prophylactic purposes. Thrombosis prevention is carried out in the presence of artificial heart valves, in patients with atrial fibrillation and a history of ischemic stroke or transient ischemic attack, etc. Indirect anticoagulants are often prescribed on the 2-3 day of heparin therapy and are used simultaneously for 2-3 days, the dose of heparin is gradually reduced until it is discontinued. Patients can take indirect anticoagulants throughout their lives.

In dentistry, indirect anticoagulants are not used, but the doctor must take into account the possibility of their use by the patient.

**Tactics of managing dental patients receiving indirect anticoagulants**

Patients taking indirect anticoagulants have an increased risk of bleeding during dental procedures, accompanied by bleeding. It should be borne in mind that paracetamol, which is often used as an analgesic for toothache, can lengthen the INR up to 4 or more, depending on the dose taken. If it is necessary to perform the operation, the drug is canceled 48 hours before the INR is assessed. Intervention is safe at INR 3.0. If it is impossible to refuse the drug (atrial fibrillation, etc.), one should be prepared for the development of bleeding

Prevention is carried out (aminocaproic acid and transexamic acid locally) bleeding or local hemostasis using a hemostatic sponge. With continued bleeding, plasma, cryoprecipitate, phytomenadione are used intravenously.

**Drugs**

*Warfarin* is the main clinically significant drug. The initial dose of the drug is selected empirically, from 2-5 mg / day, on the 2nd day it is recommended to increase the initial dose by 33-50%. Its correction is carried out on the 3-4th day after the assessment of the INR.

Available in tablets of 2.5 mg.

**Antiplatelet agents**

*Antiplatelet agents* include drugs that inhibit platelet aggregation at different levels of their activation.

**Classification**

- NSAIDs, acetylsalicylic acid
- Thienopyridines (ticlopidine, clopidogrel)
- Glycoprotein complex IIb/IIIa receptor blockers (abciximab;tirofiban, etc.)
- Dipyridamole

Platelet aggregation is also affected by a number of other drugs, such as dextrans(reopoliglyukin, polyglucin), methylxanthines (pentoxifylline). However, they are not used as independent drugs.

**Indications for use:**

- ~ prevention of arterial thrombosis in the presence of risk factors in the patient;
- ~ emergency conditions - acute coronary syndrome, transient disorders cerebral circulation.

Antiplatelet drugs are not very effective for the prevention of venous thrombosis, where the main drugs are indirect anticoagulants or heparins. Antiplatelet drugs inhibit platelet aggregation at various levels platelet activation. The best known and widely used antiplatelet agent in clinical practice is *acetylsalicylic acid* (ACA).

**Mechanism of action**

ACA irreversibly inhibits COX and blocks the synthesis of thromboxane A2 in platelets for the entire period of their life (up to 14 days). The antiaggregatory effect is manifested at low doses - 30-325 mg.

**Main clinical effects**: antiplatelet, as well as anti-inflammatory, antipyretic, analgesic, which depend on the dose.

**Pharmacokinetics**

Well *absorbed* in the gastrointestinal tract. ASA has a T1 / 2 of 15 minutes, under the influence of esterases of the stomach and liver, salicylate is cleaved from ASA, T1 / 2 of which is 4-6 hours.

*Metabolized* in the liver, excreted by the kidneys.

**Side effects:**

*GIT*: even low doses can cause mucosal changes (formation ulcers).

*Allergy*: Vidal syndrome.

**Drug Interactions**

With simultaneous use with heparin or indirect anticoagulants, the risk of bleeding increases.

**Contraindications** to the prescription of ACA:

- ~ hemorrhagic manifestations and risk factors for bleeding (preoperative, early postoperative, prenatal and postnatal periods);
- ~ gastric and duodenal ulcer in the acute stage;
- ~ agranulocytosis;
- ~ thrombocytopenia, leukopenia;
- ~ intolerance, including aspirin asthma, Vidal's syndrome.

**Management tactics for dental patients**

Performing dental procedures against the background of the use of aspirin may be accompanied by bleeding. Suturing or plugging the socket after tooth extraction usually provides good hemostasis.

**Drugs**

*Aspirin* is used at a dose of 100-325 mg/day by mouth in one dose after a meal with a glass of water for a long time. Laboratory control is not required.

Available in the form of tablets of 0.1 g, 0.25 g, 0.325 g, 0.5 g.

*Ticlopidin* (ticlid) - has a half-life of 24 hours, which, with prolonged use, is extended to 50 hours. The effect develops slowly. To control possible neutropenia (<1.5x109 l) when using ticlopidine, it is recommended to conduct a blood test every 2 weeks during the first 3 months of therapy. Take 0.25 g 2 times a day with meals. Available in tablets of 0.25 g.

*Dipyridamole* (curantil, persanthin) inhibits phosphodiesterase, which increases the content of cyclic AMP in platelets, reducing their adhesion. In terms of antiaggregation activity, it is inferior to other drugs, therefore it is used in combination with ACA.

Unlike aspirin, it does not cause ulcerative lesions of the gastrointestinal mucosa.

It is taken 75-100 mg 4 times a day.

Available in tablets of 0.025 g and 0.075 g.

**Management tactics for dental patients taking dipyridamole.**

The risk of bleeding is generally small, however, increases with the combination of dipyridamole with aspirin. During dental procedures, patients need careful monitoring. If bleeding occurs, local hemostasis is performed.

## 25.2 Antihemorrhagic agents

They are blood products (cryoprecipitate - factor VIII, frozen plasma - factors IX, X, VII, fibrinogen) and synthetic drugs (fibrinolysis inhibitors - lysine derivatives and a protease inhibitor; vitamin K preparations; drugs that affect the vascular wall). Atbleeding caused by taking heparin, its antagonist protamine is used.

Often in clinical practice, drugs with unproven efficacy are used to stop bleeding, such as vitamin C, calcium chloride, calcium gluconate, etc. This delays the identification of the causes and sources of bleeding, the use of effective drugs.

**Indications for use in dentistry:**

- ~ emergency conditions - bleeding;
- ~ bleeding and their prevention in the oral cavity (after tooth extraction and dental procedures). When performing dental procedures, accompanied by bleeding, as a rule, local methods are used.

**Classification**

The group includes the following drugs:

- ~ Fibrinolysis inhibitors (aminocaproic acid, aminomethylbenzoic acid, transexamic acid, aprotinin).
- ~ Vitamin K medications.
- ~ Drugs that affect the vascular wall (etamsylate).
- ~ Heparin antagonist protamine sulfate.

Fibrinolysis inhibitors are represented by two groups of drugs: synthetic derivatives of the amino acid lysine and protease inhibitor aprotinin.

**Mechanism of action**

Synthetic derivatives of lysine - aminocaproic acid (ACC), aminomethylbenzoic acid and transexamic acid (TEK) inhibit fibrinolysis,blocking the connection of plasminogen (plasmin) with fibrin.

Aprotinin at high doses inhibits serine proteases and calicrein, which, by activating plasminogen, accelerates fibrinolysis, and at low doses, aprotinin, like lysine derivatives, disrupts the bond between plasminogen and fibrin. Aprotinin (*trazilol, kontrykal, gordok*) should be used only during operations using cardiopulmonary bypass to reduce blood loss. Use in acute pancreatitis and other indications is not justified, as efficacy has not been proven in controlled clinical trials.

**Main clinical effects**: antifibrinolytic.

**Pharmacokinetics**

Lysine derivatives are used orally, intravenously and topically. TEK is 10 times more active than ACC and persists in tissues for a longer time. The bioavailability of TEK is 30-50%, peak serum concentration develops after 3 hours. The effect persists up to 12 hours. Excreted by the kidneys.

**Side effects:**
*GIT*: nausea, vomiting, diarrhea.
*Cardiovascular system*: hypotension. The risk of thrombosis is low.

**Clinical features of the application**

Lysine derivatives are used for bleeding caused by systemic(for example, in the postoperative period) or local fibrinolysis (bleeding after tooth extraction, nosebleeds, etc.), including in patients with hemophilia or taking indirect anticoagulants.

*Contraindications* to prescribing fibrinolysis inhibitors

- ~ severe renal dysfunction;
- ~ hypercoagulation;
- ~ tendency to thrombosis and thromboembolism;
- ~ pregnancy and childbirth;
- ~ intolerance

**Features of stopping bleeding during tooth extraction**

In the oral mucosa and saliva, there is a high content of plasminogen activator, which explains the high effectiveness of ACC and TEK in bleeding, associated with dental procedures. In patients with hemophilia, the use of ACC and TEK may prevent bleeding after tooth extraction. ACC is used at 50-60 mg / kg orally every 4 hours, TEC at 20-25 mg / kg every 8 hours orally until the bleeding from the hole stops completely. As an aqueous rinse (1g every 6 hours) TEC is effective in preventing bleeding in patients with hemophilia, who are to have a tooth extracted, as well as against the background of therapy with indirect anticoagulants.

ACC is effective for bleeding after tooth extraction, nosebleeds in patients with moderate thrombocytopenia.

**Drugs**

*Aminocaproic acid* is used orally, intravenously and topically. Inside, adults take 6 g 4 times a day, intravenously - first, a loading dose is administered 4-5 g in the first hour, then 1 g / hour.

Available in granules for oral administration and as a 5% solution for administration.

*Aminomethylbenzoic acid* (amben, pamba) is used orally at 0.25 g 3-4 times a day, intravenously 100 mg. Produced in tablets of 0.25 g, in ampoules of 5 ml with a 1% solution for injection.

*Transexamic acid* (transamcha, cyclocaprone, exacil) is used orally at 1-1.5 g 2-4 times a day and intravenously at 10-15 mg / kg, also locally. In patients with hemophilia, they are administered immediately before surgery or begin to be taken orally the day before surgery, after surgery they continue to take it for 2-8 days. In renal insufficiency, the dose of TEK is reduced. In patients taking indirect anticoagulants, to prevent bleeding, before suturing, the surgical wound is washed ex tempore with a prepared 5% solution, then rinse the mouth every 6 hours for 2 minutes for at least 2 days. After rinsing for 1 hour, you can not drink and eat.

Produced in tablets of 0.25 g and 0.5 g, in ampoules with a 10% solution.

*Vitamin K* (phytomenamidion, menadione). Fat-soluble vitamin K1 enters the body in an inactive form with green vegetables, and K2 synthesisregulated by the intestinal flora. Synthetic vitamin K preparations(phytomenamidion, menadione) are used for hypovitaminosis and as antagonists of indirect anticoagulants.

*Phytomenadione* (konakion) is a synthetic analogue of vitamin K1. When administered orally, the effect appears after 6-10 hours, with intramuscular injection - after 1 hour and lasts 3-6 hours. When administered intravenously, it can cause severe allergic reactions (collapse, bronchospasm). To stop bleeding during therapy with indirect anticoagulants, it is used intravenously and intramuscularly at 10-50 mg 3-4 times a day.

Produced in ampoules of 1 ml of a 1% solution and in capsules.

*Menadione* (Vikasol) - an inactive form of K, is absorbed in the small intestine in the presence of bile, the effect develops after 24 hours. It is used at 15-30 mg / day orally and 10-15 mg/day intramuscularly. Often mistakenly used for bleeding of a different etiology. Side effects: allergic reactions (urticaria, bronchospasm).

Available in tablets of 0.015 g and 1 ml ampoules 10 mg.

*Etamsylate* (dicynone) helps to reduce the permeability of the vascular wall. With intravenous administration, the onset of the effect is observed after 5-15 minutes, the duration of action is 4-6 hours.

It is used to prevent capillary bleeding during surgical interventions, including in dentistry. Not effective for bleeding caused by anticoagulants. Do not administer in the same syringe with other drugs. Side effects: paresthesia, epigastric pain, facial flushing, lowering blood pressure.

Available in tablets of 0.25 g, ampoules of 2 ml, 12.5% solution.

*Protamine sulfate, h*eparin antagonist, used for bleeding caused by an overdose of heparin or to neutralize heparin during operations using a heart-lung machine. The effect develops very quickly, lasting up to 2 hours.

*Side effects*: bradycardia, arterial hypotension, nausea, prolongation of the effect of muscle relaxants.

*Contraindicated* in thrombocytopenia.

It is administered at the rate of 1 mg of protamine per 100 IU of heparin, but not more than 50 mg per administration.

Produced in 1% solution in vials for injection.

## Control questions

1. For the prevention of venous thrombosis in surgery, the following is used:

a) Acetylsalicylic acid
b) Neodicumarin
c) Low molecular weight heparin
d) Dipyridamole
e) Vikasol

2. Bleeding during dental procedures may be due to taking:

a) Vitamin K
b) Ciprofloxacin
c) Aminoglycosides
d) Warfarin
e) Captopril

3. Before performing a dental procedure on a patient, taking warfarin, it is necessary to investigate:

a) Clotting time
b) Bleeding time
c) INR
d) APTT
e) Fibrinogen level

4. Dental manipulations are safe at the INR level:

a) 3.0
b) 3.5
c) 3-4
d) 4-5
e) 5-6

5. When prescribing heparin, the following can be observed:

a) Hypoglycemia
b) Aphthous stomatitis
c) Hypertension
d) Thrombocytopenia
e) Psychosis

6. As an antiplatelet agent, the following is used:

a) Ibuprofen
b) Warfarin
c) Enoxaparin
d) Aspirin
e) Vikasol

6. When using low molecular weight heparins, it is necessary:

a) Control APTT
b) Control clotting time
c) Refuse laboratory control
d) Control INR
e) Control PT

8. The use of streptokinase may be accompanied by:

a) Hypokalemia
b) Systemic bleeding
c) Ulcerative lesions of the gastrointestinal mucosa
d) Neutropenia
e) Psychosis

9. The anticoagulant effect of warfarin is enhanced by interaction with:

a) Rifampicin
b) Paracetamol
c) Vitamin B6

d) Carbamazepine
e) Metronidazole

10. To stop bleeding after tooth extraction, apply:

a) Vikasol
b) Vitamin C
c) Ca chloride
d) Protamine sulfate
e) Aminocaproic acid

# Chapter 26 Antibacterial, Antifungal, Antiviral medications

## Indications for use in dentistry

In dental practice, AMPs are second only to painkillers in terms of frequency of use. On an outpatient basis, a dentist treats patients with localized forms of odontogenic and periodontal infections; in a hospital setting, assistance is provided for common forms of infections and their complications. Decisive in the treatment of these diseases are dental manipulations and surgical aid.

AMP in dentistry is also prescribed for prophylactic purposes, for example, for the prevention of infective endocarditis when performing certain dental procedures in patients with diseases of the valvular apparatus of the heart, vascular bypass surgery, etc.

Along with this, there may be changes in the oral cavity (for example, stomatitis) as a manifestation of complications of antimicrobial therapy. Unjustified and inadequate use of AMPs can significantly affect the resistance of microflora in various loci of the body, and lead to a decrease in the effectiveness of therapy for other diseases.

## General features of antimicrobials

*AMPs* are drugs that selectively inhibit the vital activity of microorganisms. Selectivity refers to: (1) activity only against infectious agents, while saving livesthe inability of host cells, and (2) the effect on certain genera and species of microorganisms. They are divided into antibacterial, antiviral and antifungal.

All AMPs are united by a number of unique properties:

- ~ the target (receptor) of AMP is not in human tissues, but in a microorganism;
- ~ AMP activity may decrease over time due to the development of drug resistance (resistance).

Resistant pathogens pose a danger not only to the patient from whom they were isolated, but also to other people. The fight against resistance is a global challenge.

AMPs are divided into natural (actual antibiotics: penicillin), semi-synthetic (modification of natural molecules: amoxicillin, cefazolin) and synthetic (sulfonamides, nitrofurans). Today, such a systematization has lost its relevance, since a number of natural AMPs are obtained by synthesis (chloramphenicol), and some antibiotics (fluoroquinolones) are synthetic compounds.

AMPs are divided into separate groups and classes. It is not correct to consider all drugs in the same class or generation as interchangeable. Thus, among III-generation cephalosporins, only ceftazidime and cefoperazone have clinically significant activity against Pseudomonas aeruginosa, and of the fluoroquinolones, ciprofloxacin acts best on it.

For many years, AMPs have been classified according to the breadth of their spectrum of antimicrobial activity. From the standpoint of today, the division into drugs with a wide and narrow spectrum of action is conditional. When assessing the spectrum of activity, it is necessary to take into account the acquired antibiotic resistance. For example, tetracyclines, which were initially active against most clinically significant microorganisms, “lost” a significant part of their spectrum of activity due to the development of resistance in pneumococci, staphylococci, enterobacteria, etc. Cephalosporins III generations are usually regarded as drugs with a wide spectrum of activity. However, they do not act on methicillin-resistant staphylococci, enterococci, many anaerobes, chlamydia, mycoplasmas.

The following main mechanisms of bacterial resistance to AMPs are distinguished (Fig. 26.1):

a) change in the target of antibiotics;

b) enzymatic inactivation of the antibiotic;

c) active removal of the antibiotic from the microbial cell (efflux);

d) violation of the permeability of microbial cells for antibiotics;

e) formation of metabolic "shunts".

Fig. 26.1. Mechanisms of resistance to antibacterial drugs.

The mechanisms of resistance can be observed in the example of various groups of antibiotics:

a) a change in the target of action of macrolides and lincosamides due to methylation on ribosomes (this mechanism ensures the development of streptococcal resistance);

b) production of -lactamase - enzymes that destroy -lactam antibiotics. The most dangerous are extended-spectrum lactamases (ESBLs), which are more often observed in bacteria from the genus *Klebsiella* and *E. coli.* They are able to destroy penicillins and cephalosporins of all generations;

c) transport systems for removing the antibiotic from the microbial cell (efflux) in *P.aeruginosa* provide a decrease in its sensitivity to carbapenems;

d) a decrease in the permeability of a microbial cell leads to the formation of resistance to several groups of antibiotics simultaneously;

e) the appearance in bacteria of the enzyme dihydrofolate reductase, which is insensitive to inhibition by trimethoprim, which is part of co-trimoxazole, interfere with the block of synthesis of folic acid and causes resistance of bacteria and to co-trimoxazole.

Antibiotic resistance is not universal and depends on the site of infection (home, hospital), type of hospital (more often in the intensive care unit, purulent surgery), previous antibiotics, etc.

Antibiotic planning should be based on global data, regional and local resistance data. For example, in hospitals in Russia, *S. aureus* is often characterized by high methicillin resistance (up to 40%). The spread of multiresistant *P. aeruginosa*, that is, with acquired resistance to at least three antibiotics, has also been noted.

**Pharmacodynamics**

Pharmacodynamics of AMP characterizes the effect on a microorganism that is a target for AMP. This distinguishes AMP from other drugs that act on specific receptors in the human body. The effect depends on the spectrum and degree of AMP activity in relation to one or another type of microorganisms. The quantitative expression of AMP activity is its minimum inhibitory concentration (MIC): the lower it is, the more active AMP is.

In recent years, the interpretation of the pharmacodynamics of AMP has expanded. It involves the relationship between the concentration of the drug in the body and its antimicrobial activity, as well as between the time to maintain the concentration of the drug and its activity, therefore, *two groups of antibiotics* are distinguished: (1) dose-dependent and (2) time-dependent antimicrobial activity.

For the first group (aminoglycosides, fluoroquinolones), the degree of bacterial death directly correlates with the concentration of the antibiotic in the blood serum, so the goal of the dosing regimen is to achieve the maximum tolerated concentration of the drug.

For the second group, for example, -lactams, it is important to maintain the concentration at a relatively low level for a long time (4–5 times higher than the MIC). Increasing the concentration does not affect ethe effectiveness of therapy. Dosing regimens should be aimed at maintaining a concentration in the blood serum and the focus of infection that is 4-5 times higher than the MIC. It is enough that it persists for 40-60% of the time interval between injections.

According to *the type of action*, AMPs are distinguished that cause the death of a microorganism - *bactericidal fungicidal*, virucidal action and stopping the reproduction of a microorganism - *bacteriostatic, fungistatic, virostatic action*.

The same AMPs can have both "cidic" and "static" effects. This is determined by the type of microorganism, the concentration of AMP and the duration of exposure.

Thus, vancomycin has a bacteriostatic effect on streptococci, and a bactericidal effect on staphylococci. The type of action is important when choosing an AMP in various clinical situations.

Bactericidal AMPs are the drugs of choice for severe infections or in patients with immune disorders: sepsis, meningitis, endocarditis, severe head and neck infections, etc.

**Pharmacokinetics**

Of the pharmacokinetic characteristics of AMPs, the most important are the *ability to penetrate into the focus of infection* and create concentrations in it sufficient to "cid" or "static" action. Therefore, the antimicrobial activity of the drug in vitro, which is reflected in the value of the MIC, is only a guideline for ensuring clinical and microbiological efficacy.

For AMPs that are taken orally, such a parameter as bioavailability (F), i.e. *the ability to penetrate into the systemic circulation*, is of paramount importance. For example, preference for oral administration is given to amoxicillin (bioavailability 75-80%) rather than ampicillin (40%). Bioavailability is not an invariable parameter and, by creating modern dosage forms, it can be increased. For example, if amoxicillin in tablets or capsules has a bioavailability of about 75–80%, then in a special soluble form (*Flemoxin solutab*) it exceeds 90%.

The half-life ($T_{1/2}$) affects the frequency of administration of AMP. Considering that most AMPs are excreted by the kidneys, serum creatinine is determined in patients and its clearance (SC) is calculated using the Cockroft-Gault formula (Cockroft, Gault, 1976) in adults, and according to the Schwarz formula (Schwarz, 1987) in children.

$$SC\ (ml / min) = \frac{(140\text{-age}) \times \text{ideal body weight(kg)}}{0.8 \times \text{serum creatinine (µmol/l)}}$$

For women = 0.85 x QC for men

### Adverse effects

The main feature of NLR antibiotics is the effect on the normal human microflora. In most cases, changes in the microflora are not clinically manifested and do not require correction. However, in some cases, antibiotic-associated diarrhea, oral or vaginal candidiasis may develop, which requires treatment based primarily on the clinical picture.

It should be noted that the widespread opinion about the ability of these drugs to suppress the immune system is a serious misconception. All AMPs that can cause immunosuppression in humans are screened out at the stage of preclinical studies. Moreover, a number of antibiotics are able to stimulate certain parts of the immune response, for example, (macrolides, lincosamides, fluoroquinolones).

Allergic reactions to antibiotics are not fundamentally different from allergic reactions to other drugs. There are three main points to keep in mind:

The risk of allergy to antibiotics is greatly exaggerated. Does not exist "allergies to all antibiotics", as these are drugs with different chemical structures.

Allergy may be to drugs in a certain class, for example, β-lactams(penicillins, cephalosporins, etc.). Therefore, the diagnosis is absolutely incorrect: "Allergy to antibiotics."

The most common allergic reactions are to β-lactams, especially penicillins. The most important means of prevention is: (a) history taking; (b) conducting skin allergy tests to detect sensitization; (c) conducting provocative tests (if it is impossible to use another antibiotic, they are carried out by a specialist).

Antihistamines do not prevent the development of sensitization to AMP, therefore, they should not be administered together with antibiotics. Thus, there are certain similarities between AMPs of the same class or chemical group. Their appointment should take into account the characteristics of each AMP, an also results from controlled clinical trials.

## 26.1 ANTIBACTERIAL DRUGS

### Beta-lactam antibiotic

*β-lactam antibiotics* (β-lactams) that have a α-lactam ring as a common element in their chemical structure include penicillins, cephalosporins, carbapenems and monobactams. The presence of a -lactam ring causes the same mechanism of action - a violation of the formation of the bacterial cell wall and a bactericidal effect, as well as the development in some cases of cross-allergy. Penicillins and cephalosporins can be inactivated by the action of β-lactamases produced by a number of bacteria. Carbapenems are significantly more resistant to β-lactamases.

**Penicilins**

*Penicillins* are the first AMPs developed on the basis of active substances produced by microorganisms. Currently, the group of penicillins includes more than a dozen drugs, which, having a number of common properties, differ by origin, structural features, spectrum of activity and pharmacokinetics (Table.26.1).

**Table 26.1. Classification of penicillins**

| | |
|---|---|
| Natural | Benzylpenicillin (penicillin G)<br>benzylpenicillin procaine<br>Benzathine benzylpenicillin<br>Phenoxymethylpenicillin |
| Antistaphylococcal | Methicillin<br>Oxacillin |
| Spread Spectrum<br>*(Aminopenicillins)* | Ampicillin<br>Amoxicillin |
| Antipseudomonal<br>*Carboxypenicillins* | <br>Carbenicillin<br>Ticarcillin |
| *Ureidopenicillins* | Azlocillin<br>Piperacillin |
| inhibitor-protected | Amoxicillin/clavulanate<br>Ampicillin/sulbactam<br>Ticarcillin/clavulanate<br>Piperacillin/tazobactam |
| Combined | Ampicillin/oxacillin |

General properties of penicillins are bactericidal action, low toxicity, a wide range of dosages, cross-allergy between all penicillins. In some cases, there is a cross-allergy to penicillins and other β-lactams.

**Natural penicillins**

***Benzylpenicillin (PENICILLIN)***

The first natural antibiotic that continues to play an important role in the treatment of a number of infections. It has high activity against a number of clinically significant microorganisms (streptococci, meningococci, etc.) and low toxicity.

The disadvantages are the acquired resistance of staphylococci, pneumococci, gonococci, many anaerobes, as well as high allergenicity.

*Spectrum of activity*. Streptococci are the most sensitive of Gram(+) cocci (especially group A beta-hemolytic streptococcus). There are resistant strains among pneumococci, the latter often being resistant to other AMPs. Enterococci are insensitive. Most staphylococci (*S.aureus**(PRSA - penicillin-resistant (penicillin-resistant) S.aureus), *S. epidermidis*) are resistant, because they produce β-lactamases. Of the Gram(-) cocci, meningococci are highly sensitive(*N. meningitidis*). Most gonococci (*N. gonorrhoeae*) are resistant due to the production of lactamases.

Penicillin acts against listeria, diphtheria, anthrax, spirochetes.

Antianaerobic activity extends to many spore-forming(clostridia - *C. tetani, C. perfringens*) and non-spore-forming (*peptococcus, peptostreptococci*, etc.) anaerobes, actinomycetes. The presence of resistant strains among anaerobes is possible - *Prevotella spp.* and *F. nucleatum*. B. fragilis is the most common causative agent of intra-abdominal and pelvic infections and is resistant to penicillin.

*Pharmacokinetics*. Breaks down in the stomach. It is well absorbed when administered intramuscularly.

Creates high concentrations in soft tissues, but poorly penetrates through the hemato-encephalic barrier (HEB). Excreted by the kidneys. $T_{1/2}$ - 0.5 h.

*Unwanted reactions*. The most common *allergic reactions* are urticaria, rash, angioedema, fever, eosinophilia, bronchospasm. The most dangerous is anaphylactic shock. To prevent it, it is necessary to take into account the allergic history, observe the patient for 30 minutes after the first injection, and conduct skin tests (only in specialized allergological departments). With the development of clinical symptoms of anaphylactic shock, 0.5 ml of a 0.1% solution of adrenaline is immediately injected intramuscularly (deltoid muscle), then glucocorticoids (hydrocortisone 500 mg iv), antihistamine drugs (diphenhydramine 25 mg IM). If necessary, epinephrine is administered repeatedly in the same dose.

*Changes in the oral cavity* are manifested in the form of stomatitis, cheilitis, acute glossitis, blackening or lining of the tongue.

When using very high doses, with renal failure and endolumbar administration, *neurotoxic reactions* (tremor, convulsions) are possible.

*Drug interactions*. Synergism when combined with aminoglycosides in action on gram (+) cocci (can not be mixed in the same syringe or infusion system due to physico-chemical incompatibility!).

*Indications for use.* Streptococcal infections (tonsillopharyngitis, erysipelas, scarlet fever, acute rheumatic fever, necrotizing fasciitis), community-acquired pneumococcal pneumonia, meningitis in children over 2 years of age and adults bacterial endocarditis (in combination with gentamicin or streptomycin), syphilis,

leptospirosis, tick-borne borreliosis (Lyme disease), anthrax, gas gangrene, tetanus, actinomycosis.

***PHENOXYMETHYLPENCILLIN***

*The spectrum of activity does* not differ from penicillin, but is stable when taken orally. Bioavailability 60%, food does not significantly affect it. T1 / 2 1 hour Sometimes causes moderate NLR from the gastrointestinal tract (discomfort, nausea, etc.).

It is used for non-severe forms of streptococcal infections of the skin and soft tissues, tonsillopharyngitis. In dentistry, it is used for ulcerative necrotic gingivitis, periodontal abscess, odontogenic osteomyelitis, pericoronitis, cellulite.

*Extended interest derivativescillin (depot-penicillins).*This group includes benzylpenicillin procaine (novocaine salt of penicillin), with a duration of action of about 24 hours, benzathine benzylpenicillin, acting up to 3-4 weeks (*bicillin-1*) and combined preparations created on their basis (*bicillin-3, bicillin-5*). They are fine crystalline suspensions, are entered only in / m. Slowly absorbed from the injection site, do not create high concentrations in the blood. Do not penetrate the HEB.

*Unwanted effects*. Possible *infiltrates* at the injection site. *Vascular complications* are specific: ischemia and gangrene of the extremities in case of injection into artery; embolism of the vessels of the lungs and the brain when injected into a vein, damage to the sciatic nerve. For the prevention of vascular complications, strict adherence to the technique of administration is necessary.

They are used for syphilis and for the prevention of rheumatic fever.

*Antistaphylococcal penicillins.* Representatives of this group of penicillins are resistant to the action of penicillinase(from the α-lactamase group), which is produced by 80-90% of *S. aureus* strains.

***OXACILLIN***

The main clinical significance is the activity against PRSA. The rest is inferior to penicillin. A serious problem is the spread of strains of S. aureus, resistant to oxacillin (methicillin *), called MRSA (methicillin-resistant S. aureus).

Bioavailability when taken orally - 20-30%, which is further reduced after eating. It is better to use parenterally. It is excreted by the kidneys and with bile. T1 / 2 0.5 h.

*Unwanted reactions*. See benzylpenicillin. Sometimes noted *hepatotoxicity* (increased activity of liver transaminases, more often when used in high doses and in children) and *hematotoxicity*.

*Indications for the use* of staphylococcal infections (except those caused by MRSA). At dentistry is used for staphylococcal infections of the soft tissues of the maxillo-facial area and neck, osteomyelitis of nonodontogenic origin.

**Penicillins with an extended spectrum of activity**

***AMPICILLIN***

*Spectrum of activity*. Unlike natural and anti-staphylococcal penicillins, it acts on aerobic gram (-) enterobacteria (E. coli, Salmonella, Shigella) and *H. influenzae*, but many resistant strains have recently emerged. In terms of action on streptococci, meningococci, spirochetes, anaerobes, it is approximately equal to penicillin. PRSA and most gram(-) pathogens of nosocomial infections are resistant.

*Pharmacokinetics*. Bioavailability when taken on an empty stomach 30-40%, after a meal almost 2 times lower. Poorly passes through the BBB. It is excreted in urine and bile, creating high concentrations in them. $T_{1/2}$ - 1 hour

*Unwanted reactions*. See benzylpenicillin. From the gastrointestinal tract, pain is possible, nausea, vomiting, diarrhea. 5-10% of patients may develop an "*ampicillin*" rash of a non-allergic nature, having a maculopapular character, not accompanied by itching and disappearing without discontinuation of the drug. Risk factors for rash: infectious mononucleosis, cytomegaly, chronic lymphocytic leukemia, concomitant use of allopurinol.

*Indications for use*. Community-acquired infections of the lower and upper respiratory tract, meningitis, bacterial endocarditis (in combination with gentamicin or streptomycin), salmonellosis, biliary tract infections, leptospirosis.

In dentistry, it is used when it is impossible to take amoxicillin orally.

AMOXICILLIN

An ampicillin derivative with improved pharmacokinetics (Table 26.2). The most commonly used oral antibiotic in the world. The spectrum of activity is similar to ampicillin, it has a better effect on pneumococcus and *Helicobacter pylori*.

*Pharmacokinetics*. When taken orally, it is absorbed faster and is 2-2.5 times better than ampicillin. Bioavailability (up to 95%) does not depend on food. Creates higher and more stable concentrations in the blood and bronchopulmonary secretions. It is actively secreted with gastric juice and creates a high concentration in it. In the lower gastrointestinal tract, drug concentrations are low (not used for intestinal infections). Excreted with urine. $T_{1/2}$ 1-1.3 h.

*Unwanted reactions*. See ampicillin. Diarrhea occurs much less frequently.

*Indications for use*. See ampicillin, H. pylori eradication, tick-borne borreliosis, prevention of bacterial endocarditis and anthrax. In dentistry, it is widely used for odontogenic and periodontal infections, maxillary odontogenic sinusitis.

**Table 26.2. Comparative characteristics of ampicillin and amoxicillin**

| | Ampicillin | Amoxicillin |
|---|---|---|
| Activity against pneumococcus | ++ | +++ |
| H. pylori | + | +++ |
| Ways of insertion | Inside, in / m, in / in | inside |
| Absorption in the gastrointestinal tract | 40% | 75-95% |
| The effect of food on bioavailability | ↓ twice | Does not affect |
| Level in sputum | low, unstable | high, stable |
| Adverse reactions | Diarrhea (often) | Diarrhea (rare) |

**Antipseudomonal penicillins**

The main feature of carboxypenicillins (carbenicillin, ticarcillin) and ureidopenicillins (azlocillin, piperacillin) have long been active against *P. aeruginosa*. Their spectrum of activity also includes enterobacteria: E. coli, Proteus, etc., Gram (+) cocci. All antipseudomonal penicillins are destroyed by β-lactamases, including staphylococcal ones. They are used only parenterally.

Currently, due to the high level of secondary resistance of *P. aeruginosa*, these drugs have lost their importance. Practically not used in dental practice.

*Unwanted reactions*. See benzylpenicillin. May cause impaired platelet aggregation and electrolyte shifts (hypernatremia, hypokalemia).

**Inhibitor-protected penicillins**

The main mechanism of bacterial resistance to β-lactams is their production of β-lactamases, which destroy the β-lactam ring. This protective mechanism is one of the leading ones for gram (+) cocci, gram (-) bacteria (*E. coli, Klebsiella spp*.), anaerobes (*B. fragilis*, etc.). Clavulanic acid (clavulanate), sulbactam, tazobactam inhibit -lactamases. Based on them, combined drugs have been created, called inhibitor-protected penicillins.

***AMOXICILLIN/CLAVULANATE***

Consists of amoxicillin and potassium clavulanate. The ratio of components in preparations for oral administration is 2:1, 4:1 and 8:1, for parenteral administration - 5:1.

*Spectrum of activity*. It acts on all microorganisms sensitive to amoxicillin, as well as on gram (-) flora that produces β-lactamase (*H. influenzae, M. catarrhalis, E. coli, Klebsiella,* etc.) and almost all anaerobes, including *B. fragilis*.

*Pharmacokinetics*. Well absorbed when taken orally, food has little effect on bioavailability. It is well distributed in the body and creates high concentrations in tissues and secretions, including the lungs, middle ear, sinuses. Excreted by the kidneys. $T_{1/2}$ - 1.2 hours

*Unwanted reactions*. See amoxicillin. Due to the presence of clavulanate, dyspeptic disorders and an increase in transaminase activity are possible.

*Indications for use*. See amoxicillin. In addition: nosocomial pneumonia, intra-abdominal and pelvic infections, infections of the skin, soft tissues, bones, joints, biliary and urinary tract, sepsis, perioperative antibiotic prophylaxis.

In dentistry, it is used for infections of the maxillofacial region and neck (putrefactive necrotic phlegmon of the face and neck, phlegmon of deep cellular spaces of the neck), with complications of odontogenic infections.

***AMPICILLIN/SUlbactam***

Consists of ampicillin and sulbactam in a ratio of 2:1. Practically does not differ in antimicrobial spectrum from amoxicillin / clavulanate, having similar indications.

***PIPERACILLIN/TAZOBACTAM***

Consists of piperacillin and tazobactam in a ratio of 8:1. Active against *P. aeruginosa*, many nosocomial strains of enterobacteria, anaerobes. It is entered only in / in. It is used for nosocomial infections.

**Combined penicillins**

***AMPICILLIN/OXACILLIN***

A combination of ampicillin and oxacillin in ratios of 1:1 (for oral administration) and 2:1 (for parenteral administration). Outdated drug.

***CEPHALOSPORIN***

The advantage of cephalosporins is bactericidal action, low toxicity. Depending on the spectrum of activity, cephalosporins are divided into four generations (Table 26.3)

**Table 26.3. Classification of cephalosporins**

| | I | II | III | IV |
|---|---|---|---|---|
| Parenteral | Cefazolin | Cefuroxime | Cefotaxime | Cefepime |
| Oral | Cephalexin | Cefuroxime axetil | Cefixime | Ceftriaxone |
| | | Cefaclor | Ceftibuten | Ceftazidime |
| | | | | Cefoperazone |
| | | | | Cefoperazone /Sulbactam |

**Table 26.4. Comparative spectrum of activity of cephalosporins**

| | CLINICALLY SIGNIFICANT ACTIVITY | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Pathogens | | | | |
| Streptococcus spp. | + | ++ | +++ | +++ |
| S. pneumoniae | + | + | +++ | +++ |
| Staphylococcus spp. (PRSA) | +++ | +++ | ++ | +++ |
| H. influenzae | - | ++ | +++ | +++ |
| M. catarrhalis | - | ++ | +++ | +++ |
| E. coli | + | ++ | +++ | +++ |
| P. mirabilis | + | ++ | +++ | +++ |
| Klebsiella spp. | - | + | +++ | +++ |
| Shigella spp. | - | + | +++ | +++ |
| Salmonella spp. | - | + | +++ | +++ |
| Pseudomonas aeruginosa* | - | - | ++ | ++ |
| Anaerobes | - | - | - | - |

* Active ceftazidime, cefoperazone, cefepime

*Unwanted reactions*. In general, cephalosporins are well tolerated. Sometimes *allergic reactions* can be observed - urticaria, measles rash, fever, etc. The risk of their development, especially to first-generation cephalosporins, is increased in patients allergic to penicillins. Cross-allergy occurs in 5-10% of cases. If there is a history of allergic reactions of an immediate type (urticaria, anaphylactic shock, etc.) to penicillins, cephalosporins of the first generation should not be used. In doubtful cases, you can start treatment with a trial dose of the oral drug. May be noted leukopenia,

increased activity of transaminases, gastrointestinal symptoms (pain, nausea, vomiting, diarrhea).

**I generation cephalosporins**

They have a narrow antimicrobial spectrum. Greatest clinical significance have activity against streptococci and staphylococci, excluding MRSA and enterococci.

***CEFAZOLIN***

The main cephalosporin of the I generation.

*Activity spectrum*: works on streptococci, staphylococci (including PRSA). MRSA, enterococci, most strains of hemophilus and enterobacteria are resistant.

Pharmacokinetics: administered parenterally 2-3 times a day. Poorly penetrates through the HEB. Excreted unchanged mainly in the urine (80%) and partially in the bile. $T_{1/2}$ - 2 hours.

*Indications for use*: Streptococcal and staphylococcal infections of the skin, soft tissues, bones and joints; perioperative antibiotic prophylaxis.

***CEFALEXIN***

Oral cephalosporin. Bioavailability - 95%, $T_{1/2}$ - 1 hour. Used for tonsillopharyngitis, skin infections, soft tissues, bones, joints.

**II generation cephalosporin**.

***CEFUROXIM, CEFUROXIM AXETIL***

*Spectrum of activity*: The effect on gram(+) cocci is similar to that of cefazolin. More active against Gram(-) bacteria: *E. coli, H. influenzae, M. catarrhalis* etc.

*Pharmacokinetics*: well distributed in the body, penetrating into many organs and tissues, pass through the BBB during inflammation of the meninges. Excreted mainly in the urine. $T_{½}$ - 1.5 hours.

Cefuroxime axetil is a prodrug, cefuroxime ester for oral administration. In the process of absorption, is hydrolyzed with the release of cefuroxime. Bioavailability when taken during or immediately after a meal is higher (50-70%) than on an empty stomach (37%).

*Indications for use*: otitis media; sinusitis; community-acquired pneumonia; skin infections, soft tissues, bones, joints, urinary tract; perioperative antibiotic prophylaxis; step-by-step therapy.

**III generation cephalosporins**

High activity against gram (-) enterobacteria, including many nosocomial strains. Some of the drugs (ceftazidime, cefoperazone) act on Pseudomonas aeruginosa. III

generation cephalosporins were initially used only in hospital settings for the treatment of severe infections. In severe and mixed infections, they must be used in combination with metronidazole, sometimes with vancomycin.

***CEFOTAXIM***

The first "basic" III generation cephalosporin.

*Spectrum of activity*. Among gram (+) cocci, streptococci are the most sensitive (including many penicillin-resistant pneumococci). Highly active against gonococci, meningococci, *M. catarrhalis, H. influenzae*, many gram (-) enterobacteria (E. coli, Proteus, Klebsiella, etc.). Activity against anaerobes is low.

*Pharmacokinetics*: pass well through the HEB. Excreted by the kidneys. $T_{1/2}$ - 1 hour.

*Indications for use*: sinusitis; community-acquired and nosocomial pneumonia; severe infections of the urinary tract, skin, soft tissues, bones, joints; intestinal infections (shigellosis, salmonellosis); intra-abdominal and pelvic infections (in combination with anti-anaerobic drugs); meningitis; sepsis.

***CEFTRIAXONE***

The spectrum of activity is similar to that of cefotaxime. It is used for all the same indications. Differences from cefotaxime: significantly longer $T_{1/2}$ - 5-7 hours (the longest among all cephalosporins), so it can be used once a day, a double route of excretion - with urine and bile, so dose adjustment is not required for renal failure.

***CEFTAZIDIM***

Differences from cefotaxime: high activity against *P. aeruginosa*; weaker effect on gram (+) cocci (streptococci, staphylococci); longer $T_{1/2}$ - 2 hours.

*Indications for use*: nosocomial infections, including Pseudomonas aeruginosa.

***CEFOPERAZONE, CEFOPERAZONE/SUlBACTAM***

*Differences from cefotaxime*: acts on *Pseudomonas aeruginosa*; excreted from the body with bile and urine (dosage adjustment is not required for renal failure); penetrates worse through the BBB; $T_{1/2}$ - 2 hours; may cause hypoprothrombinemia; has a disulfiram-like effect.

Indications for use: see cefotaxime (except meningitis and gonorrhea).

**Table 26.5. Comparative characteristics of cefotaxime, ceftriaxone, ceftazidime and cefoperazone**

| | Cefotaxime | Ceftriaxone | Ceftazidime | Cefoperazone |
|---|---|---|---|---|
| Activity spectrum | | | | |

| | | | | |
|---|---|---|---|---|
| *S. aureus* | +++ | +++ | + | ++ |
| *S. pneumonia* | +++ | +++ | + | ++ |
| *P. aeruginosa* | - | - | +++ | ++ |
| Frequency of administration (times a day) | 3-4 | 1-2 | 2-3 | 2-3 |
| Passage through the HEB | ++ | ++ | ++ | + |
| Treatment of meningitis | Yes | Yes | Yes | No |
| Disulfiram-like effect | No | No | No | Yes |
| Hypoprothrombinemia | No | No | No | Yes |

Cefoperazone/sulbactam is a 1:1 combination of cefoperazone and the β-lactamase inhibitor sulbactam. It is used for severe forms of community-acquired infections and nosocomial infections, including anaerobic infections.

**IV generation cephalosporins**

IV generation cephalosporins include CEFEPIME, which has a higher resistance to the action of β -lactamases produced by nosocomial strains of enterobacteria than the drugs of previous generations. Active against *P. aeruginosa*.

It is used for severe, predominantly nosocomial infections.

***CARBAPENEMS***

*Carbapenems* have structural similarity with other β-lactamases, but have wider spectrum of activity, including many strains of gram (-) bacteria, resistant to cephalosporins III-IV generations, Pseudomonas aeruginosa and anaerobes; characterized by high resistance to the action of extended-spectrum β-lactamases. To carbapenems include imipenem and meropenem. They are used for severe community-acquired and nosocomial infections caused by multidrug-resistant microorganisms and mixed flora, including anaerobes.

***IMIPENEM***

Used in combination with cilastatin in a 1:1 ratio. Cilastatin is an inhibitor of the renal enzyme dehydropeptidase I. When used without cilastatin, imipenem is destroyed by this enzyme and does not create therapeutic concentrations in the urine.

**Table 26.6. Carbapenems versus III-IV generation cephalosporins**

| | Carbapenems | Cephalosporin |
|---|---|---|
| Activity spectrum | | |
| Gram(-) ESBL-producing bacteria | +++ | - |
| MRSA | - | - |
| Enterococci | ++* | - |
| Anaerobes | +++ | + |
| Cross-resistance with other β -lactams | No | Possible |
| Monotherapy | Usually | Not always** |

ESBL - extended spectrum β -lactamase

* imipenem only for E. faecalis,

** Often used in combination with metronidazole and/or aminoglycosides

*Pharmacokinetics*. Well distributed in the body. It passes through the BBB during inflammation of the meninges. Excreted by the kidneys. T1 / 2 - 1 hour. It is used in / in only drip.

*Unwanted reactions*. Sometimes symptoms of neurotoxicity (tremor, convulsions), especially in the elderly, when using high doses, rapid administration, in patients with severe diseases of the central nervous system, renal failure.

***MEROPENEM***

Differences from imipenem: more active against gram( ) flora; weaker effect on staphylococci and streptococci, does not have proconvulsant activity (can be used for meningitis).

***TETRACYCLINES***

The main representatives of tetracyclines are the natural antibiotic tetracycline and the semi-synthetic drug doxycycline. General properties are bacteriostatic action, a wide spectrum of activity and a high incidence of NLR.

*Spectrum of activity*. Tetracyclines have a very wide natural spectrum of activity, but at present, activity against chlamydia, mycoplasmas, Helicobacter, Yersinia, propionobacteria, spirochetes, rickettsia, pathogens of especially dangerous infections (cholera, anthrax, brucellosis, plague, tularemia), tropical malaria. Many strains of *S. pneumoniae* and *H. influenzae* are resistant to tetracyclines.

*Pharmacokinetics*. Doxycycline has a high bioavailability of 90-100%, independent of food. Create high concentrations in dentin, enamel, fluid in the gingival groove. Poorly pass through the BBB, to a high extent penetrate the placenta and into breast milk. Excretion of tetracycline is carried out mainly through the kidneys, doxycycline - through the gastrointestinal tract. T1 / 2 tetracycline 8 hours, doxycycline - 15-24 hours.

*Unwanted reactions*. More common with tetracycline. From the gastrointestinal tract: glossitis with atrophy of the papillae and blackening of the tongue, stomatitis, xerostomia, esophagitis, abdominal pain, nausea, vomiting, diarrhea. Violation of the formation of bone and dental tissue (slowdown of linear bone growth, discoloration of teeth, enamel defects). When using tetracyclines in the 2nd half of pregnancy or in infants, there may be changes in milk teeth. If tetracyclines were used during the formation of tooth enamel (at the age of 2 months to 8 years), then discoloration of permanent teeth and enamel defects are possible. Allergic reactions (rash, urticaria, etc.), symptoms of hepatotoxicity, nephrotoxicity, photosensitivity (often causes doxycycline), brain pseudotumor syndrome.

*Drug interactions*. Antacids containing Ca, Mg, Al cations, iron preparations reduce the bioavailability of tetracyclines due to the formation of insoluble complex compounds. Carbamazepine and barbiturates reduce the concentration of doxycycline in the blood. Tetracyclines reduce the effect of estrogen-containing oral contraceptives, due to impaired hydrolysis of estrogen conjugates in the intestine, occurring with the participation of bacterial flora.

*Indications for use*. The use is limited due to the high level of resistance and the risk of adverse reactions. Used to treat chlamydia rickettsiosis, acne, travelers' diarrhea. In dentistry, they are used in the treatment of actinomycosis, lymphadenitis of the cervicofacial region associated with cat scratch disease. A mixture of tetracycline and lidocaine in the form of a syrup can be used for the local treatment of aphthous stomatitis, ulcerative necrotic gingivitis. Can be used in 1-2 doses for periodontitis.

*Contraindications for use*. Age up to 8 years, pregnancy, breastfeeding, severe liver pathology, renal failure (tetracycline).

***MACROLIDES***

The basis of the structure of this group of AMPs is a macrocyclic ring. At depending on the number of carbon atoms in the ring, they are divided into 14-membered (erythromycin, clarithromycin, rocksithromycin), 15-membered (azithromycin) and 16-membered(midecamycin, spiramycin, josamycin).

*General properties*. They have a bacteriostatic effect, moderate immunomodulatory, anti-inflammatory and prokinetic effects.

*The spectrum of activity* includes gram (+) cocci (streptococci, staphylococci, except MRSA), some anaerobes (*Peptostreptococcus spp., Peptococcus spp*.), intracellular microbes (chlamydia, mycoplasma, legionella, campylobacter),

spirochetes, diphtheria bacillus, pertussis pathogen. Azithromycin is more active against *H. influenzae, M. catarrhalis*, clarithromycin - against *H. pylori*. Cross-resistance to erythromycin and clarithromycin is possible. Coccal flora resistant to 14- and 15-mer macrolides may remain sensitive to 16-mer ones (spiramycin, midecamycin).

*Pharmacokinetics*. Absorption in the gastrointestinal tract depends on the drug, its dosage form and food intake. The bioavailability of erythromycin, azithromycin, midecamycin is reduced in the presence of food. Concentrations of macrolides in tissues are much higher than in blood serum, high intracellular concentrations are observed. Macrolides cross the placenta and into breast milk. Metabolized in the liver, excreted mainly through the gastrointestinal tract.

*Azithromycin* is also often referred to as a special class of antibiotics - *azalides*.

*Unwanted reactions*. Well tolerated. Possible dyspeptic disorders, hepatotoxicity (more often when using erythromycin, less commonly with spiramycin and josamycin). Rarely allergic reactions (rash, urticaria), prolongation of the QT interval. Clarithromycin may alter the sense of taste.

*Drug interactions*. Macrolides (mostly erythromycin and clarithromycin) inhibit the metabolism of indirect anticoagulants, theophylline, carbamazepine, cyclosporine, etc. You can not combine macrolides with cisapride due to the risk of developing severe cardiac arrhythmias. Rifampicin enhances the metabolism of macrolides.

*Indications for use*. Respiratory tract infections, especially those caused by atypical pathogens (mycoplasmas, chlamydia, legionella), *H. pylori* eradication (clarithromycin), urogenital chlamydia, acne. In pregnant women, erythromycin, spiramycin can be used. In infections of the maxillofacial region and neck, macrolides are prescribed for allergies to β-lactams, they can serve as an alternative to tetracycline and clindamycin in mild forms of skin infections. Clarithromycin and spiramycin in combination with metronidazole are effective and safe in odontogenic infections. In the treatment of periodontitis, spiramycin was superior in efficacy to erythromycin and tetracycline, especially when combined with metronidazole.

***ERYTHROMYCIN***

Of clinical importance is activity against gram (+) cocci, chlamydia, mycoplasmas, legionella, campylobacter. In recent years, the emergence of erythromycin-resistant pneumococcus and pyogenic streptococcus has been noted. Bioavailability - from 30 to 65% and decreases in the presence of food. T1 / 2 1.6–2.5 hours. Often causes dyspeptic disorders.

***CLARITHROMYCIN***

Greater stability in the gastrointestinal tract, higher bioavailability (55%), independent of food intake. T1 / 2 3-7 hours. High activity against *H. pylori*.

***AZITHROMYCIN***

Better effect on gram (-) flora - especially H. influenzae. Stable in acidic environment creates higher concentrations in tissues. Bioavailability 40%, little dependent on food, long $T_{1/2}$ 55 hours. It is possible to conduct short courses of therapy (1-3 days), causes fewer NLRs and drug interactions.

***SPIRAMYCIN***

Stable in an acidic environment, bioavailability does not depend on food, high and stable concentrations in tissues; long $T_{1/2}$; causes fewer ADRs, no drug interactions. Contained in high concentrations in saliva, penetrates deep into the gums and alveolar processes.

***LINCOZAMIDES***

*Lincosamides* (lincomycin, clindamycin) have a bacteriostatic effect, caused by inhibition of protein synthesis by ribosomes of a microbial cell.

*The spectrum of activity* of gram (+) cocci (staphylococci), peptostreptococci, fusobacteria, actinomycetes, gram (-) anaerobes, pigment-forming anaerobes, etc.), as well as *B. fragilis*.

*The activity of clindamycin* is much higher than that of lincomycin.

*The bioavailability of clindamycin* is significantly higher (90%) and does not depend on food intake. High concentrations are achieved in bone tissue.

*Metabolized* in the liver. $T_{1/2}$ 2.5-3 hours, 2 times shorter than lincomycin, does not change with renal failure.

*Unwanted reactions*. The most common symptoms are abdominal pain, diarrhea, nausea, vomiting, glossitis. Pseudomembranous colitis is the main reason for limiting the use of lincosamides. If pseudomembranous colitis is suspected liquid stools with an admixture of blood) it is necessary to cancel the drug, conduct sigmoidoscopy, correct the water and electrolyte balance, prescribe antibiotics, active against *C. difficile* (metronidazole or vancomycin).

*Drug interactions*. May increase neuromuscular blockade in combination with inhaled drugs or muscle relaxants (anticholinesterase drugs, calcium chloride are used to eliminate them). Respiratory depression is possible when combined with opioid analgesics. Absorbent antidiarrheal drugs (attapulgite) reduce the absorption of lincosamides in the gastrointestinal tract, so 3-4 hour intervals between doses of drugs. Do not combine with chloramphenicol or macrolides due to their antagonism.

*Indications for use*. They are used for streptococcal tonsillopharyngitis with allergies to penicillins. Aspiration pneumonia, infections of soft tissues, bones and joints, intra-abdominal infections, infections of the small pelvis., locally at bacterial vaginosis and acne.

In dentistry, lincosamides are more commonly used in patients with β-lactam allergy. Clindamycin can be used to prevent endocarditis during manipulations in the oral cavity, as an alternative to amoxicillin.

***NITROIMIDAZOLES***

Nitroimidazole derivatives include metronidazole, tinidazole, ornidazole. At mainly differ in the duration of $T_{1/2}$, therefore they have different dosing regimens.

***METRONIDAZOL***

Antianaerobic drug. The resistance of the anaerobic flora is noted very rarely.

Spectrum of activity. Acts on spore-forming (clostridia, including *C. difficile*) and non-spore-forming anaerobes. Anaerobic cocci are somewhat less sensitive - peptostreptococci, peptococcus. Therefore, with an odontogenic infection, it is better to combine metronidazole with β-lactams. Active against protozoa (Trichomonas, Giardia, amoeba, etc.) and *H. pylori*.

*Pharmacokinetics*. Bioavailability when taken orally is 80% and is practically independent of food. It is well distributed in the body, therapeutic levels are determined in the mucous membranes, pleural exudate, abscess cavities, and the brain. Actively secreted with saliva. Metabolized in the liver, excreted in the urine and stool. T1 / 2 6-8 hours, does not change with renal failure.

*Unwanted reactions*. From the digestive tract: glossitis, stomatitis, metallic taste, xerostomia, nausea, anorexia. Neurotoxicity: incoordination, irritability, insomnia, tremors, convulsions. Sometimes transient neutropenia, thrombocytopenia. disulfiram-like effect. Causes a teratogenic effect, should not be used in the first trimester of pregnancy.

*Drug interactions*. Metronidazole inhibits the metabolism of indirect anticoagulants. A decrease in the concentration of metronidazole in the blood with a weakening of the effect is observed with the simultaneous use of phenobarbital, phenytoin or rifampicin.

*Indications for use*: anaerobic infections; infections of the skin, soft tissues, bones; brain abscesses; eradication of *H. pylori* (in combination with antisecretory drugs, amoxicillin or clarithromycin), protozoal infections (trichomoniasis, giardiasis, amoebiasis); pseudomembranous colitis; perioperative antibiotic prophylaxis in abdominal surgery and gynecology.

In dentistry, metronidazole in combination with -lactams is used for odontogenic infection (pulpitis, periodontitis). The drug of choice for the treatment of ulcerative gingivitis.

***TINIDAZOL, ORNIDAZOL***

According to *the spectrum of activity*, the nature of NLR and indications, they are similar to metronidazole.

They have a longer $T_{1/2}$ (12-14 hours). Ornidazole has no disulfiram-like effect.

***SULFANILAMIDES AND CO-TRIMOXAZOL***

*Sulfonamides* (SA) are the oldest class of AMPs, but have lost their importance in recent years. in clinical practice, as they are significantly inferior in activity to modern antibiotics and have high toxicity. Are not used in dental practice.

*Mechanism of action*. SA have a bacteriostatic effect. Structurally similar to para-aminobenzoic acid (PABA), therefore, they competitively inhibit the bacterial enzyme responsible for the synthesis of the folic acid precursor, necessary for the life of bacteria. In environments where there is a lot of PABA (pus), SA activity is significantly reduced.

*Spectrum of activity*. Many gram(+) and gram(-) were initially sensitive bacteria, but they currently have a high level of resistance. They remain active against nocardia, toxoplasma, pneumocystis, malarial plasmodia.

*Pharmacokinetics*. SA (except non-absorbable) are well absorbed in the gastrointestinal tract, especially when taken on an empty stomach in crushed form. The highest concentrations in blood serum create preparations of short and medium duration of action. SA crosses the placenta into breast milk. Metabolized in the liver, excreted mainly in the urine. Accumulate in renal failure.

*Undesirable reactions* develop frequently. Severe allergic reactions are possible in the form of Stevens-Johnson syndrome and Lyell's syndrome; hematotoxic (agranulocytosis, thrombocytopenia, etc.); hepatotoxic (hepatitis) and neurotoxic reactions, etc.

*Drug interactions*. Increase the concentration in the blood of indirect anticoagulants, anticonvulsants, oral hypoglycemic agents. With simultaneous administration with penicillins, the effect of the latter is reduced.

*Indications for use*: toxoplasmosis, pneumocystis pneumonia, nocardiosis.

*Contraindications*: Should not be prescribed for renal failure, severe liver dysfunction and anemia, children under 2 months, pregnant.

***CO-TRIMOXAZOLE (SULFAMETOXAZOLE/TRIMETHOPRIM)***

Currently, the combined preparation CO-TRIMOXAZOL, which contains in a ratio of 5: 1, has clinical significance for systemic use.

Sulfamethoxazole and trimethoprim, which blocks the metabolism of folic acid (breaks the formation of tetrahydrofolic acid) and has a bactericidal effect.

It is used for urinary tract infections; shigellosis (in regions with a low level of pathogen resistance); staphylococcal infections, including those caused by MRSA

(reserve drug); infections caused by *S. maltophilia*, *B. cepacia*, etc. (see. sulfonamides). It is rarely used in dental practice (sinusitis and sialadenitis).

***GLYCOPEPTIDES***

*Glycopeptides* include VANCOMYCIN.

*The spectrum of activity* includes gram (+) aerobic and anaerobic microorganisms: staphylococci (MRSA, MRSE), streptococci, enterococci, clostridia (including *C. difficile*).

Vancomycin is administered intravenously by drip or orally (for pseudomembranous colitis). $T_{1/2}$ 6-8 hours Possible reversible nephrotoxicity, dizziness, headache, hearing loss, vestibular disorders. With rapid intravenous administration of vancomycin, a reaction develops in the form of reddening of the face and upper body (syndrome of the “red man”), skin itching, chest pain, tachycardia, arterial hypotension. The reason is the release of histamine during the rapid administration of vancomycin. At the injection site, phlebitis, pain, burning are possible.

*Drug interactions*. With simultaneous use with local anesthetics, the frequency of histamine reactions increases. The risk of nephrotoxicity and ototoxicity increases when combined with aminoglycosides and furosemide.

*Indications for use*. Infections caused by MRSA, enterococci, resistant to ampicillin and aminoglycosides. Severe infections of the maxillofacial region and neck.

***QUINOLONS AND FLUOROQUINOLONES***

Synthetic AMPs with bactericidal properties due to DNA replication disorders.

Quinolones are divided into four generations (Table 26.7).

*I generation*(non-fluorinated quinolones) has a narrow spectrum of activity, including a limited number of gram (-) bacteria, are characterized by low concentrations in the blood and tissues. Subsequent generations are represented by fluorinated quinolones (fluoroquinolones).

*II generation* drugs act on a significantly larger number of gram (-) microorganisms, staphylococci.

*III generation* drugs, highly active against gram(-) bacteria, have a better effect on pneumococci and intracellular pathogens, and IV – in addition to this, on anaerobes.

**Table 26.7. Classification of quinolones**

| I generation (non-fluorinated quinolones) | II generation "gram-negative" | III generation "respiratory" | IV generation "respiratory-antianaerobic" |
|---|---|---|---|
| Nalidixic acid | Ciprofloxacin | Levofloxacin | Moxifloxacin |

| | |
|---|---|
| Oxolinic acid | Norfloxacin |
| Pipemidic acid | Ofloxacin |
| | Pefloxacin |
| | Lomefloxacin |

First generation quinolones have previously been used for urinary tract infections. Currently, fluoroquinolones are used instead.

***FLUOROQUINOLONS***

*Activity spectrum*: gram(+)cocci (except MRSA), gram (-) enterobacteria (E. coli, salmonella, shigella, proteus), Pseudomonas aeruginosa (ciprofloxacin, levofloxacin), intracellular microorganisms (Campylobacter, Legionella, chlamydia, mycoplasmas - levofloxacin, moxifloxacin); anaerobes (moxifloxacin), Mycobacterium tuberculosis (ciprofloxacin, levofloxacin, moxifloxacin).

*Pharmacokinetics*: high oral bioavailability; penetrate well into various organs and tissues, creating high intracellular concentrations; long $T_{1/2}$, which makes it possible to prescribe them 1-2 times a day.

*Unwanted reactions*. Dyspeptic reactions. Rare: prolongation of the QT interval, photosensitivity (lomefloxacin, sparfloxacin), tendonitis, arthropathy.

*Contraindicated* in pregnant and lactating women, due to the inhibition of the development of cartilage tissue in the fetus. Fluoroquinolones are prohibited for use in children.

*Drug interactions*. Absorption of fluoroquinolones in the gastrointestinal tract with simultaneous use is caused by: antacids containing Ca, Mg, Al (by 80-90%); cytoprotectors (sucralfate); preparations containing iron and zinc. ciprofloxacin, norfloxacin and pefloxacin inhibit the metabolism of theophylline, caffeine and indirect anticoagulants. Risk of tendon rupture when combined with glucocorticoids.

*Indications for use*. Exacerbation of chronic bronchitis, pneumonia, infections of the urinary tract, skin, soft tissues, bones, joints, intra-abdominal, pelvic infections and intestinal infections (shigellosis, salmonellosis, cholera), sepsis, gonorrhea, anthrax. In dentistry, the use of fluoroquinolones is limited. The most commonly used is ciprofloxacin (rarely ofloxacin). As an alternative drug, it can be used for maxillary osteomyelitis of Pseudomonas aeruginosa, abscesses, phlegmon, lymphadenitis, etc.

***CIPROFLOXACIN***

The "gold standard" of fluoroquinolones.

*Bioavailability* 80%. Partially metabolized in the liver. $T_{1/2}$ 4-6 hours.

***OFLOXACIN***

More active than ciprofloxacin against chlamydia, but has a weaker effect on Pseudomonas aeruginosa. It has a high bioavailability of 95-100%. T ½ 5-7 hours

***PEFLOXACIN***

Slightly less active than ciprofloxacin and ofloxacin. Bioavailability is about 100%. Better than other fluoroquinolones penetrates through the HEB. T 1/2 9-13 hours

***NORFLOXACIN*** is used only by mouth, mainly for urinary tract infections.

III generation quinolones are characterized by higher than in II generation quinolones, activity against pneumococci (including penicillin resistant) and intracellular pathogens (chlamydia, mycoplasmas) - the most common pathogens of respiratory tract infections. Therefore, they are sometimes referred to as "respiratory quinolones".

***LEVOFLOXACIN*** is the main representative of III generation quinolones, which is the levorotatory isomer of ofloxacin. Has a high bioavailability of about 100%. T 1/2 6-8 hours. It is used for acute sinusitis, exacerbation of chronic bronchitis, community-acquired and nosocomial pneumonia, infections of the urinary tract, skin and soft tissues.

A distinctive feature of the IV generation quinolone MOXIFLOXACIN is its high activity against non-spore-forming anaerobes, including B. fragilis. In terms of action on respiratory pathogens, it surpasses the quinolones of previous generations.

*Bioavailability* when taken orally - 90%, T1 / 2 12-13 hours. Indications for use are the same, like levofloxacin.

***AMINOGLYCOSIDES***

*Aminoglycosides* have a bactericidal effect, which is due to a violation of protein synthesis by ribosomes. The antimicrobial effect depends on the maximum concentration in the blood. Aminoglycosides are toxic, but allergic reactions are rare. A pronounced synergism of action is manifested in relation to a number of gram (+) and gram (-) aerobes when used together with penicillins and cephalosporins.

The main clinical significance lies in the activity against aerobic gram(-) bacteria causing nosocomial infections (amikacin), mycobacterium tuberculosis (streptomycin, kanamycin). They are used for the prevention and treatment of infective endocarditis, for prophylaxis in colorectal surgery. There are three generations of aminoglycosides (Table 26.8).

**Table 26.8. Classification of aminoglycosides**

| I GENERATION | II GENERATION | III GENERATION |
|---|---|---|
| Streptomycin | Gentamicin | Amikacin |
| Neomycin | Netilmicin | |
| Kanamycin | | |

*Spectrum of activity*. Of clinical importance is the high sensitivity to aminoglycosides of II-III generations of Enterobacteriacea (E. coli, Proteus, Klebsiella, enterobacter, etc.), P. aeruginosa and some other non-fermenting bacteria.

Streptomycin, kanamycin and amikacin are active against Mycobacterium tuberculosis. Of the Gram(+) cocci, staphylococci, including PRSA, are the most susceptible. Streptococci and enterococci are moderately sensitive. Aminoglycosides are not active against pneumococci, anaerobes and atypical microorganisms.

*Pharmacokinetics*. They are practically not absorbed in the gastrointestinal tract, therefore they are administered parenterally. Compared to β-lactams, aminoglycosides pass through various tissue barriers (including HEB). The highest concentrations were found in the kidneys and urine. Aminoglycosides are not metabolized and are excreted unchanged by the kidneys. $T_{1/2}$ with normal kidney function is 2-3.5 hours, with renal failure it can increase several times.

*Unwanted reactions*. The most characteristic are ototoxicity (vestibulo- and / or cochleatotoxicity), nephrotoxicity and the development of neuromuscular blockade. The frequency of nephrotoxic reactions in patients treated with aminoglycosides over 7 days, reaches 26%, the development of renal failure is possible. The most severe manifestation of neuromuscular blockade is paralysis of the respiratory muscles. Neurotoxicity manifests itself in the form of drowsiness, paresthesia, tremor, convulsions.

Streptomycin may cause burning, numbness, or paresthesia in the face and mouth.

*Prevention of adverse reactions* consists in the prescription of aminoglycosides strictly according to indications; in doses not exceeding the maximum daily allowance, in compliance with the maximum duration of the course - 7-10 days; the appointment of only one aminoglycoside at a time; at a repeated course not earlier than in 4-6 weeks. Aminoglycosides should not be prescribed to patients with myasthenia gravis, botulism. It is necessary to monitor kidney function (determination of serum creatinine with calculation of glomerular filtration) before the appointment of an aminoglycoside and then every 2-3 days, hearing and function of the vestibular apparatus.

*Principles of dosing of aminoglycosides*. The dose calculation is carried out taking into account the body weight and age of the patient, kidney function and localization of infection. The modern dosing regimen involves a single administration

of the entire daily dose (preferably by intravenous drip), which, compared with 2-3 times the introduction does not reduce the effectiveness and safety of therapy.

Since aminoglycosides are not distributed in adipose tissue, their doses calculated for ideal weight should be reduced by 25% for obesity, and increased by 25% for underweight.

With a decrease in glomerular filtration rate, it is necessary to reduce the daily dose by either (1) reducing the single dose of the drug, or (2) increasing the intervals between injections.

*Indications for use*. Gram(-) flora infections (aminoglycosides II-III generations); enterococcal infections (gentamicin or streptomycin in combination with penicillin or ampicillin) tuberculosis (streptomycin, amikacin, kanamycin - always in combination with other anti-tuberculosis drugs); especially dangerous infections.

Neomycin and gentamicin are part of ointments, eye and ear drops. With this use, a toxic resorptive effect is also possible.

In dental practice, aminoglycosides are used only for severe gram (-) nosocomial infections (amikacin), for the prevention of endocarditis at the maximum regimen (gentamicin) in combination with ampicillin or vancomycin.

***STREPTOMYCIN*** is the first aminoglycoside introduced into clinical practice. Currently used limitedly only for tuberculosis, bacterial endocarditis (in combination with penicillin or ampicillin), zoonotic infections.

***NEOMYCIN*** is the most toxic of the aminoglycosides. It is applied only locally.

***KANAMYCIN*** is an outdated drug with a high oto- and nephrotoxicity. Retains its value in tuberculosis as a reserve drug.

***GENTAMICIN*** is the main aminoglycoside of the second generation. It is used for nosocomial pneumonia, urinary tract infections, intra-abdominal and pelvic infections (in combination with antianaerobic drugs), bacterial endocarditis (in combination with penicillin or ampicillin), sepsis.

***AMIKACIN*** is active against many strains of gram (-) bacteria, P. aeruginosa, resistant to aminoglycosides II generation, tuberculosis mycobacteria (an anti-tuberculosis drug of the reserve group). It is used for multidrug-resistant gram(-) infections.

Aminoglycosides are dosed per kilogram of body weight: streptomycin, kanamycin, amikacin - 15-20 mg / kg / day in 1-2 injections; gentamicin, tobramycin - 3-5 mg / kg / day in 1-2 introductions; netilmicin - 4-6.5 mg / kg / day.

***CHLORAMPHENICOL***

*Clinical use* is currently limited due to the risk of serious adverse reactions, primarily from the blood. It has a bacteriostatic effect, which is associated with a violation of protein synthesis by ribosomes.

Initially, it had a wide spectrum of activity, but now many microorganisms are resistant. Retains activity against anaerobic flora (including B. fragilis). Used to treat meningitis, brain abscess, intra-abdominal, small pelvis. Chloramphenicol is rarely used in dentistry.

Well absorbed in the gastrointestinal tract, food does not affect bioavailability. It penetrates well through the HEB, the placenta, into breast milk. Metabolized in the liver. In renal failure, dose adjustment is not required. $T_{1/2}$ in adults is 1.5-3.5 hours, in children up to 6.5 hours.

*Unwanted reactions*. Hematological reactions: a) reversible (dose-dependent): reticulocytopenia, thrombocytopenia, anemia, leukopenia; b) irreversible - aplastic anemia. Newborns have a “gray syndrome” (vomiting, respiratory distress, cyanosis, collapse, hypothermia, acidosis). Glossitis and stomatitis may develop.

**Proprietis of the choice of antibiotics for infections of the oral cavity, maxillofacial area and neck**

The choice of AMP for dental infections depends on its localization (oral cavity, soft tissues, etc.), relation to anatomical structures (periodontium, gum, mucosa, etc.), stage of development (with odontogenic infections), severity of the course.

Odontogenic infections (infections of the oral cavity), depending on the anatomical structures, are divided into true odontogenic, associated with damage to the tissues of the tooth (caries, pulpitis); periodontal associated with periodontal disease (periodontitis) and gums (gingivitis, pericoronitis), surrounding tissues (periosteum, bone, soft tissues of the face and neck, maxillary sinus, lymph nodes); nonodontogenic origin, associated with lesions of the mucous membranes (stomatitis) and inflammation of the large salivary glands.

These types of infection can cause serious life-threatening complications in the brain, mediastinum and other localizations, as well as disseminated hematogenous damage to the valvular apparatus of the heart and sepsis.

Purulent infection of the face and neck of non-odontogenic origin includes folliculitis, furuncle, carbuncle, hematogenous osteomyelitis of the jaws, etc. The facial area may also be manifestations of specific infections (actinomycosis, tuberculosis, syphilis, HIV).

*Infections associated with the oral cavity* are associated with the constantly present microflora. Since it is quite difficult to isolate a specific causative agent of a certain odontogenic infection, in the overwhelming majority of cases, empirical antibiotic therapy is carried out, aimed at the most likely infectious agents and taking

into account their most likely sensitivity to AMP. Outpatient practice treatment of non-severe localized infections *odontogenic* origin is often limited to standard dental procedures.

Systemic antibiotic therapy is carried out only when the process spreads under the periosteum, into the bones of the jaws, soft tissues of the face and neck, as well as with the development of a systemic reaction (fever, intoxication, lymphadenitis). As a rule, AMPs are administered orally. When the infection is localized in the maxillofacial region and neck, surgical intervention is decisive. Taking into account possible pathogens, preference is given to - lactams (amoxicillin, amoxicillin/clavulanate) and anti-anaerobic (metronidazole, lincosamides) drugs.

In the treatment of patients with neutropenia, immunodeficiency states, nosocomial infections, AMPs with an extended spectrum of activity are used: CS II-IV generations, fluoroquinolones, carbapenems, glycopeptides.

**Pulpitis**

The main pathogens are green streptococci (S. mutans, S. milleri). As the infection progresses, the anaerobic flora of Peptostreptococcus spp., Fusobacterium spp. and etc.

Usually, patients do not need to take AMPs. If necessary, drugs of choice are prescribed: phenoxymethylpenicillin 0.5 g every 6 hours orally.

*Alternative drugs*: amoxicillin/clavulanate, clindamycin, metronidazole, macrolides.

*The duration* of therapy depends on the severity of the course, but should be at least 5 days.

**Periodontal infections**

In *periodontal infections*, five pathogens are most often isolated: P. gingivalis, P. intermedia, E. corrodens, F. nucleatum, A. actinomycetemcomitans.

**Periodontitis**

The causative agents of periodontitis in adults are gram-negative anaerobes and spirochetes. *Treatment is usually limited to dental manipulation*. At juvenile age, there is a rapid development of the process involving bone tissue.

*Drugs of choice*: amoxicillin + metronidazole.

*Alternative drugs*: amoxicillin/clavulanate, 2nd generation cephalosporins, macrolide + metronidazole, doxycycline. *The duration of therapy is at least 5-7 days*.

In patients with leukemia, the drugs of choice are cephalosporins II-IV generations + metronidazole, cefoperazone / sulbactam; piperacillin/tazobactam or

ticarcillin/clavulanate aminoglycosides; carbapenems. *Duration of therapy* is at least 10-14 days.

Odontogenic periostitis and osteomyelitis, osteogenic (traumatic) osteomyelitis of the jaws.

Anaerobic flora predominates among the causative agents of periostitis and odontogenic osteomyelitis: P. niger, Peptostreptococcus spp, Bacteroides spp., Prevotella spp. At 50% cases, S. aureus and Streptococcus spp. are isolated, less often A. israelii, T. pallidum. In osteogenic (traumatic) osteomyelitis, S. aureus is more often isolated, less often enterobacteria and P. aeruginosa.

*Drugs of choice*: amoxicillin/clavulanate, ampicillin/sulbactam.

*Alternative drugs*: lincosamides, cefuroxime. When isolating S. aureus -oxacillin, MRSA - vancomycin. P. aeruginosa - ceftazidime, ciprofloxacin.

*The duration of therapy* should be at least 4-8 weeks.

**Buccal cellulitis**

Usually seen in children under 5 years of age. H. influenzae (type B) and S. pneumoniae. In children under the age of 2 years, the main causative agent is H. influenzae, in this case, as a rule, bacteremia is observed.

*Drugs of choice*: amoxicillin/clavulanate, third-generation cephalosporins (cefotaxime, ceftriaxone), IV in high doses.

*Alternative drugs*: co-trimoxazole.

**Abscesses, phlegmons of the face and neck**

With abscesses and phlegmons of odontogenic origin in the region of the orbit, neck in adults, anaerobes (Peptostreptococcus spp, Bacteroides spp., Veillonella spp., Fusobacterium spp., Eikenella spp.) and coccal gram(+) flora (Staphylococcus spp.. Streptococcus spp.). In children, staphylococci and streptococci predominate.

Severe lesions in elderly and hospitalized patients are associated with facultative Gram(-) flora (Enterobacteriaceae) and S. aureus. With putrefactive necrotic phlegmon of the floor of the mouth (Ludwig's angina), face and neck, a polymicrobial flora is distinguished (Eikenella spp., Bacteroides spp., Peptostreptococcus spp., Streptococcus spp., Actinomyces spp.). Against the background of diabetes mellitus, alcoholism, gram (-) enterobacteria, P. aeruginosa, S. aureus and S. pyogenes are the causative agents of abscesses and phlegmon of non-odontogenic origin (more often in the presence of minor lesions).

*Drugs of choice*: inhibitor-protected penicillins.

*Alternative drugs*: cefazolin + metronidazole, lincosamides ± oxacillin,

penicillin, vancomycin, carbapenems. When isolating P. aeruginosa, ceftazidime, cefepime aminoglycosides II-III generation, ciprofloxacin.

**Necrotizing stomatitis (ulcerative necrotic gingivostomatitis Vincent)**

Anaerobes, spirochetes are concentrated in the gingival groove; in patients with AIDS, Campylobacter rectus is a common causative agent of gingivitis. With necrotizing stomatitis, there is a tendency for the infection to spread rapidly into surrounding tissues.

*Drugs of choice:* metronidazole, phenoxymethylpenicillin, penicillin.

*Alternative drugs*: tetracyclines, amoxicillin/clavulanate, macrolide +metronidazole, lincosamides.

*The duration of therapy* depends on the severity of the course.

**Acute odontogenic maxillary sinusitis**

The causative agents in adults are non-spore-forming anaerobes (Peptostreptococcus spp, Bacteroides spp.), S. pneumoniae, H. influenzae. Isolation of S. aureus, P. aeruginosa, and other gram(-) bacteria is characteristic of nosocomial sinusitis. Children usually present with acute non-odontogenic sinusitis associated with a viral infection of the upper respiratory tract.

*The drug of choice* is amoxicillin / clavulanate, with nosocomial sinusitis - III-IV generation cephalosporins + metronidazole.

*Alternative drugs*: carbapenems; cefuroxime, cephalosporins III–IV generations + vancomycin, levofloxacin, moxifloxacin.

*Duration of therapy*: 10-14 days.

In infections of the skin, soft tissues and bones of the maxillofacial region and neck of non-odontogenic origin, S. aureus, S. pyogenes are most often isolated.

**Furuncle and carbuncle of the face and neck**

The main causative agent is S. aureus. Isolation of MRSA is possible with nosocomial infection. Recurrent boils are typical for patients with obesity, diabetes mellitus, on the background of corticosteroid therapy and immunodeficiency states.

With single elements outside the zone of the nasolabial triangle, antibiotics, as a rule, are not indicated. With a boil in the area of the nasolabial triangle, systemic antibiotic therapy is carried out, due to the threat of developing thrombophlebitis of the facial veins and thrombosis of the cavernous sinus. With furunculosis, *therapy lasts* up to 1-2 months.

*Drugs of choice*: oxacillin, amoxicillin/clavulanate, cephalosporins I-II generations.

*Alternative drugs*: in the isolation of MRSA - vancomycin, co-trimoxazole, linezolid. Topical treatment includes mupirocin, chlorhexidine.

**Lymphadenitis in the face and neck**

Regional lymphadenitis can have a different etiology (odontogenic and non-odontogenic). In children aged 1-4 years, lymphadenitis, localized on the anterior and posterior surface of the neck, is usually associated with a viral infection, abscessing of the lymph nodes is usually due to the addition of a bacterial infection. With unilateral lateral lymphadenitis over the age of 4 years, GABHS and S. aureus. Anaerobic pathogens - Bacteroides spp., P. niger, Peptostreptococcus spp., F. nucleatum, P. acnes, can cause lymphadenitis against the background of complications of caries and diseases of the oral mucosa. With lymphadenitis at the site of cat scratches, the causative agent is Bartonella henselae.

Antibiotics should be *the drugs of choice* corresponding to the etiology of the primary focus of infection and the severity of clinical symptoms (phenoxymethylpenicillin, macrolides).

Antibiotic therapy is usually continued for at least 10-14 days, regardless of surgery.

**Actinomycosis**

The causative agents of actinomycosis are Actinomyces israelii, gram (+) anaerobic bacteria, much less often - other actinomycetes. Actinomycetes form mycelium, which was the reason for their erroneous classification as fungi. However, actinomycetes do not have a nucleus, are sensitive to antibiotics (penicillins, tetracyclines) and are resistant to antifungal drugs.

*Drugs of choice*: penicillin at a dose of 18-24 million units per day parenterally for 3-6 weeks, with positive dynamics - switching to phenoxymethylpenicillin (2 g / day) or amoxicillin (3-4 g/day) for 6-12 months.

*Alternative drugs:* doxycycline 0.2 g/day, erythromycin 2 g/day.

The reasons for the low effectiveness of therapy may be insufficient *duration of therapy*, when the antibiotic course is interrupted with a decrease in clinical symptoms. It can also cause recurrence of the disease.

**Features of the choice of antibiotics for complications of infections of the face and neck**

Patients with complicated dental infections need antimicrobial therapy in a hospital, intensive care unit and intensive care unit.

**Sepsis**

The main causative agents of sepsis are gram (+) and gram (-) aerobes (S. aureus, E. coli, Klebsiella spp., Pseudomonas spp.). Therapy includes cephalosporins III-IV generation, inhibitor-protected penicillins, aminoglycosides, carbapenems, fluoroquinolones. If MRSA is suspected, vancomycin is used.

**Mediastinitis**

Mixed flora is of etiological importance, including primarily gram (-) and gram (+) aerobes (Staphylococcus spp., Enterbacteriaceae, P. aeruginosa) and anaerobes.

Combination therapy consists of III-IV generation cephalosporins or fluoroquinolones in combination with metronidazole, cefoperazone/sulbactam, or carbapenems.

**Thrombophlebitis of the facial veins and thrombosis of the cavernous sinus**

The main pathogens are S. aureus, streptococci and gram (-) anaerobes (Bacteroides spp., Fusobacterium spp.). Drugs of choice: oxacillin, cephalosporins III-IV generations in combination with antianaerobic drugs (chloramphenicol, metronidazole).

**Meningitis**

Develops as acarbuncle, phlegmon of the floor of the mouth and neck, phlegmon of the face, sometimes as a complication of maxillary sinusitis. The spread of infection is possible by the hematogenous route after surgical interventions on the sinuses of the upper jaw. The main pathogens are staphylococci, streptococci, H. influenzae, S. pneumoniae. With nosocomial infection, S. aureus, gram (-) sticks are isolated.

*The drugs of choice* are III-IV generation cephalosporins in combination with antistaphylococcal antibiotics. If a Pseudomonas aeruginosa infection is suspected, it is necessary to prescribe ceftazidime, cefepime, with MRSA - vancomycin, with anaerobic infection - inhibitor-protected penicillins, metronidazole, chloramphenicol.

**Odontogenic brain abscess**

The main pathogens are anaerobes (Prevotella spp., Bacteroides spp.) and green streptococci (S. intermedius, S. anginosus, S. constellatus).

*Drugs of choice*: penicillin + metronidazole, ceflosporins III-IV + metronidazole.

*Alternative drugs*: meropenem.

**Antibiotic prophylaxis in dentistry and face and neck surgery**

The prophylactic systemic administration of antibiotics during dental procedures in somatically healthy patients does not lead to a decrease in the incidence of infectious complications.

Carrying out dental procedures accompanied by bleeding (tooth extraction, tartar removal, prophylactic manipulations, intraligamentary anesthesia), increased gum bleeding in patients with valvular pathology or artificial heart valves is associated with the risk of developing bacterial endocarditis. The effectiveness of antibiotic prophylaxis of endocarditis in this group of patients has been proven.

**Table 29.8. Conditions requiring prophylaxis of bacterial endocarditis during dental procedures (Recommendations of the International Society for Chemotherapy, 1998)**

| | |
|---|---|
| High risk groups | Artificial heart valves |
| | Congenital "blue" heart defects |
| | History of infective endocarditis |
| Usual risk groups | Pathology of the heart valves (isolated stenosis mitral valve is discussed)<br>- aortic regurgitation<br>- mitral regurgitation<br>- aortic stenosis<br>- mitral valve prolapse with mitral regurgitation |
| | Congenital heart defects (excluding defects interatrial septum), not accompanied by cyanosis |
| | Hypertrophic obstructive cardiomyopathy |

**Table 26.10. Antibiotic prophylaxis regimens for bacterial endocarditis (Recommendations of the International Society for Chemotherapy, 1998)**

| | | |
|---|---|---|
| | 1 hour before the procedure | 6 hours after the procedure |

| | | |
|---|---|---|
| Maximum mode<br>No allergy to penicillin<br>Allergy to penicillin | Amoxicillin - 3.0 g inside<br>Clindamycin - 0.3-0.6 g inside | Not<br>Not |
| *Permissible*<br>Additional doses after manipulation<br>Additional use of aminoglycosides<br>Administration of antibiotics parenterally | | |
| Maximum mode<br>No allergy to penicillin<br><br>Allergy to penicillin | Ampicillin - 2.0 g IV + gentamicin 1.5 mg/kg IM, IV<br>Vancomycin 1.0 g IV + gentamicin 1.5 mg/kg IM, IV | Amoxicillin 1-1.5 g inside<br>Vancomycin 1.0 g IV within an hour (after 12 hours) |

Usually, in dental practice, the minimum mode is used. It should be noted that convincing data on the sufficient effectiveness of topical antibiotics in oral infections have not been obtained.

**Features of the choice of antibiotics in general clinical practice**

**Erysipelas**

Superficial cellulitis caused by group A β-hemolytic streptococcus (S. pyogenes). Often localized in the face.

*Drugs of choice*: phenoxymethylpenicillin, benzylpenicillin.

*Alternative drugs* for allergy to β-lactams: macrolides, lincosamides.

**Infections after bites of humans, animals (cats, dogs, rats)**

The causative agents of infections after a human bite are: green streptococci, coagulase-negative staphylococci, Eikenella corrodens, bacteroids, peptostreptococci.

Dog bite infections are also characterized by Pasteurella multocida, Capnocytophaga spp.; cat bite - Pasteurella.multocida S. aureus; rats - Streptobacillus moniliformis.

*Drugs of choice*: amoxicillin/clavulanate.

*Alternative drugs*: human bites - clindamycin, cefoperazone/sulbactam; dogs - ciprofloxacin + lincosamides; cats - cefuroxime axetil, doxycycline; rats - doxycycline.

**Acute otitis media**

The causative agents of acute otitis media are: S. pneumoniae, H. influenzae, M. catarrhalis.

*Drugs of choice*: amoxicillin, amoxicillin/clavulanate.

*Alternative drugs* are azithromycin, clarithromycin.

**Acute tonsillopharyngitis**

The most common viral etiology. The main bacterial pathogen is S. pyogenes.

*Drugs of choice*: phenoxymethylpenicillin for 10 days.

*Alternative drugs*: macrolides, lincosamides. For recurrent tonsillopharyngitis, amoxicillin/clavulanate is prescribed.

**Peritonsillar abscess**

Etiology polymicrobial: gram (+) cocci (S. aureus, S. pyogenes) in combination with anaerobes of the oral cavity. Surgery is of the utmost importance.

*Drugs of choice*: penicillin, amoxicillin/clavulanate.

*Alternative drugs*: lincosamides, cefuroxime, cefotaxime, ceftriaxone + metronidazole.

**Exacerbation of chronic bronchitis**

In adults, the main pathogens are S. pneumoniae, H. influenzae, M. catarrhalis, viruses. Antibacterial therapy is prescribed only for severe clinical symptoms (increased cough, purulent sputum, an increase in its volume). In acute bronchitis, antibiotics are not prescribed.

*Drugs of choice*: amoxicillin, amoxicillin/clavulanate.

*Alternative drugs*: cefuroxime, macrolides, "respiratory" fluoroquinolones (levofloxacin, moxifloxacin), doxycycline.

**Community-acquired pneumonia in adults**

At home, the main pathogens are S. pneumoniae and atypical pathogens (Mycoplasma pneumoniae and Chlamydophila pneumoniae).

*Drugs of choice*: amoxicillin, macrolides.

*Alternative drugs*: amoxicillin / clavulanate, "respiratory" fluoroquinolones.

**Kidney and urinary tract infection**

Cystitis, pyelonephritis.

The main pathogens are: E. coli and other enterobacteria.

*Drugs of choice*: fluoroquinolones.

*Alternative drugs*: cystitis - fosfomycin trimetamol, nitrofurantoin; pyelonephritis - amoxicillin / clavulanate, III-IV generation cephalosporins.

## 26.2. ANTIVIRAL DRUGS

**Indications for use in dentistry**

Infections of the skin and mucous membranes caused by herpes simplex and herpes zoster viruses. Chemoprophylaxis of parenteral HIV infection.

**Classification**

Currently, the group of antiviral drugs is relatively small. All available drugs can be divided into several groups:

- ~ antiherpetic;
- ~ anticytomegalovirus;
- ~ anti-influenza;
- ~ extended spectrum: lamivudine, ribavirin, interferons;
- ~ antiretroviral drugs (ARP).

**ANTIHERPETIC AND ANTICYTOMEGALOVIRUS**

**Drugs**

This group includes acyclovir, valaciclovir, penciclovir, famciclovir, ganciclovir and foscarnet.

*Mechanism of action*. In infected cells, activation to acyclovir triphosphate occurs, which inhibits viral replication. Foscarnet forms inactive complexes with the DNA polymerase of the herpes virus and CMV.

*Spectrum of activity*. The most sensitive viruses are herpes simplex (H.simplex) type I and II. Cytomegalovirus (ganciclovir and foscarnet).

*Pharmacokinetics*. Acyclovir, valaciclovir and famciclovir are administered orally, acyclovir, ganciclovir - in / in, penciclovir - externally. Valaciclovir is converted to acyclovir after oral administration. Famciclovir is metabolized to penciclovir when taken orally.

**Table 26.11. Pharmacokinetic characteristics of antiherpetic drugs**

| Drug | Bioavailability, % | $T_{1/2, hour}$ | Metabolism, excretion |
|---|---|---|---|
| Acyclovir | 10–20 | 2-3 | 60-90% is excreted by the kidneys inunchanged |
| Valaciclovir | 54 | 1-2 | Same |
| Famciclovir | 77 | 2 | Same |

*Drug interactions*. Cimetidine increases the blood concentration of valaciclovir. Cyclosporine and amphotericin B - increase the concentration of ganciclovir in serum.

*Indications.* Therapy and prevention of infections caused by HSV types 1 and 2, varicella-zoster virus, CMV.

*Contraindications*. Hypersensitivity to the drug, breast-feeding, pregnancy.

*Features of clinical use in various categories of patients*. At pregnant women and children can only be prescribed acyclovir. With a decrease in kidney function and in old age, dose adjustment may be required.

*Unwanted reactions*. Acyclovir is well tolerated, rarely adverse reactions from the gastrointestinal tract. Ganciclovir in 20-40% of patients causes reactions from the blood. For foscarnet, nephrotoxicity is more characteristic.

**Anti-flu drugs**

There are two groups of anti-influenza drugs: M2 channel blockers(amantadine, rimantadine) and viral neuraminidase inhibitors (zanamivir, oseltamivir).

*Mechanism of action*. Rimantadine blocks the M2 channels of the group A virus, disrupting its ability to enter cells. Zanamivir, oseltamivir, inhibiting viral neurominidase, disrupt the ability of viruses to penetrate into healthy cells and the release of virions. Neuraminidase inhibitors reduce the systemic manifestations of a viral infection (fever, etc.). spectrum of activity. Rimantadine is active against influenza A virus, zanamivir, oseltamivir - influenza viruses A and B.

*Pharmacokinetics*. Oseltamivir, unlike zanamivir, has a higher oral bioavailability.

**Table 16.12. Pharmacokinetic characteristics of anti-influenza drugs**

| Drug | Bioavailability, % | $T_{1/2, hour}$ | Metabolism | Clearance |
|---|---|---|---|---|
| Rimantadine | 90 | 25-36 | Not metabolized | Kidneys |

| | | | | |
|---|---|---|---|---|
| Oseltamivir | 80-90 | 7-8 | Liver (produced active metabolite) | kidneys |
| Zanamivir | Introduced by inhalation | 2.5–5 | - | kidneys |

*Unwanted reactions*. Rimantadine rarely causes reactions from the gastrointestinal tract and central nervous system. Zanamivir - bronchospasm, CNS damage (headache, dizziness), sinusitis. Oseltamivir - disorders of the gastrointestinal tract, damage to the central nervous system.

*Drug interactions*. Anticholinergics and antihistamines may increase the risk of CNS reactions.

*Indications*. Prevention and treatment of influenza.

*Contraindications*. Allergic reactions, breastfeeding.

*Features of clinical use in various categories of patients*. Rimantadine is not recommended in children under 1 year of age. In the elderly, dose reduction is necessary.

## DRUGS WITH EXTENDED SPECTRUM OF ACTIVITY

This group includes ribavirin, lamivudine and interferons. The most widely used antiviral drugs are recombinant alpha interferons (Intron, Roferon).

*Mechanism of action.* The mechanism of antiviral action of ribavirin has not been fully elucidated. Interferon disrupts the penetration of a viral particle into a cell, inhibits the synthesis of mRNA and translation of viral proteins, blocking the process of assembling a viral particle.

*Spectrum of activity.* Ribavirin is active against RS virus, hepatitis C virus.

*Pharmacokinetics*. The bioavailability of ribavirin is 45%. T1 / 2 30-60 h.

*Metabolized* in the liver. It is excreted mainly through the kidneys.

*Unwanted reactions*. Direct contact with the drug may cause a rash, irritation of the skin and mucous membranes. With systemic administration - anemia, lymphocytopenia, fatigue, insomnia. Interferon - flu-like syndrome (80%), anemia, thrombocytopenia, depression, alopecia.

*Drug interactions*. Magnesium and aluminum compounds reduce the bioavailability of ribavirin. Interferon inhibits the metabolism of many drugs.

*Indications*. Ribavirin - RS-viral infection, Lassa fever, HFRS, viral hepatitis C. Interferon - chronic hepatitis B, acute and chronic hepatitis C.

*Contraindications*. Hypersensitivity, severe renal and hepatic insufficiency. Pregnancy, breastfeeding.

*Features of clinical use in various categories of patients*. Ribavirin is teratogenic and is therefore contraindicated in pregnancy.

## ANTIRETROVIRAL DRUGS (ARP)

### Classification

- ~ HIV nucleoside reverse transcriptase inhibitors (NRTIs): zidovudine, mphosphazid, stavudine, didanosine, zalcitabine, abacavir
- ~ Non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs): nevirapine, ifavirenz.
- ~ HIV protease inhibitors (PIs): saquinavir, indinavir, ritonavir, nelfinavir, amprenavir
- ~ Combination drugs (lamivudine/zidovudine)

*Mechanism of action*. NRTIs block HIV reverse transcriptase and selectively inhibit viral DNA replication. NNRTIs block RNA- and DNA-dependent polymerase. PIs block the active site of the HIV protease.

### Pharmacokinetics.

**Table 26.13. Pharmacokinetic characteristics of some ARPs**

| Drug | Bioavailability, % | $T_{1/2, hour}$ | Metabolism | Clearence |
|---|---|---|---|---|
| Zidovudine | 65 | 1.1 | Liver (P450) | kidneys |
| Ifavirenz | 40 | 40-55 | Liver (inductor P450) | kidneys |
| Indinavir | 65 | 1.5-2 | Liver (P450 inhibitor) | kidneys |

*Unwanted reactions*. Poor tolerability of ARP is one of the most important reasons for low therapy compliance and high rate of ARP withdrawal. For NRTIs, mitochondrial toxicity, lactic acidosis, peripheral neuropathy, bone marrow suppression; for NNRTIs - CNS lesions; for IP - lipodystrophy, hyperlipidemia, nephrolithiasis.

*Drug interactions*. Do not prescribe drugs from the NRTI group, that are analogues of the same nucleotide. It is necessary to pay attention to whether ARP is an inducer, inhibitor or substrate of the cytochrome P450 system.

*Indications*. Treatment and prevention of HIV infection.

*Contraindications*. Hypersensitivity, breastfeeding, pregnancy, renal, liver failure.

*Features of clinical use in various categories of patients.* The appointment of zidovudine to pregnant women infected with HIV significantly reduces the risk of

infection of the child. Zidovudine, didanosine are approved for use in children. stavudine, abacavir, nelfinavir, ritonavir, ifavirenz, amprenavir, zalcitabine, saquinavir.

### CHEMIOPROPHYLAXIS OF PARENTERAL HIV INFECTION

It is used when medical workers receive injuries. entom, contaminated with HIV. If more than 72 hours have passed since the possible infection, chemoprophylaxis is considered inappropriate. The scheme is chosen depending on the characteristics of the patient-source of HIV infection.

*Basic regimen*: zidovudine 0.6 g/day in 2-3 doses + lamivudine 0.15 g every 12 hours.

*Extended regimen*: one of the basal regimens + indinavir 0.8 g every 8 hours or nelfinavir 0.75 g every 8 hours or 1.25 g every 12 hours or ifavirenz 0.6 g once a day or abacavir 0.3 g every 12 h.

## 26.3. ANTIFUNG MEDICINES

### Indications for use in dentistry

In dental practice, antifungal drugs are most often used topically for the treatment of oral candidiasis, which refers to superficial candidiasis. The latter are characterized by damage to the mucous membranes (oral cavity, esophagus, vagina) and skin. With impaired immunity, the infection acquires a chronic course, and can go into a systemic form with damage to internal organs. The most severe form is invasive candidiasis. In case of systemic lesions, in addition to C.albicans, pathogens such as Aspergillus spp., Rhizopus spp., Fusarium spp. and other mushrooms.

Yeast fungi of the genus Candida are permanent inhabitants of the oral cavity. Against the background of the use of antibiotics and immune disorders (diabetes mellitus, oncological diseases, taking immunosuppressive drugs, HIV infection), they can cause oral candidiasis, which manifests itself in the form of aphthous stomatitis, candidal leukoplakia, "prosthetic" stomatitis, drug-induced stomatitis and mucocutaneous forms of injury. Cadidal stomatitis can be a manifestation of a systemic fungal infection.

### Classification

Antifungal drugs, depending on the chemical structure, are divided into several groups differing in the spectrum of activity, pharmacokinetics, portability and indications for use (see tab. 26.14).

**Table 26.14. Classification of antifungal drugs**

| GROUPS | | REPRESENTATIVES |
|---|---|---|
| Polyena | | Nystatin |
| | | Natamycin |
| | | Amphotericin B<br>Liposomal Amphotericin B |
| Azoles | For systemic use | Ketoconazole |
| | | Fluconazole |
| | | Itraconazole |
| | For topical application | Clotrimazole<br>Miconazole |
| | | Bifonazole |
| Allylamines | | Terbinafine |
| | | Naftifin |
| Echinocandins | | Caspofungin |

The value of drugs such as potassium iodide, griseofulvin, chlornitrophenol, flucytosine is now significantly reduced.

## DRUGS OF THE POLYENES GROUP

Includes amphotericin B, nystatin, natamycin. Levorin has lost its clinical significance.

*Pharmacodynamics*. The mechanism of action is associated with a violation of the synthesis of ergosterol of the cell membrane of the fungus.

### *NYSTATIN*

A narrow spectrum drug that acts only on yeast-like fungi of the genus Candida.

*Pharmacokinetics*. Practically not absorbed in the gastrointestinal tract, with skin surface and intravaginal application. The effect is shown only at direct contact with mushrooms. Not effective for the prevention of candidiasis.

*Unwanted reactions*. Well tolerated. When taken orally in high doses - dyspeptic disorders.

*Indications*. Candidiasis of the mucous membranes of the oral cavity, esophagus, intestines, vagina. Skin candidiasis. In dentistry, it is used in the form of a suspension of 100,000 units / ml, ointments 100,000 IU/g; with candidiasis of the oral cavity and pharynx, dissolve 1 tablet (500,000 ED) every 6-8 hours after meals.

### *NATAMYCIN*

Compared with nystatin, it has a wider spectrum of activity: fungi of the genus Candida and Fusarium. It is applied topically and internally.

*Indications*. Candidiasis of the nasal cavity, mouth, intestines and skin, vulvovaginal candidiasis, balanoposthitis, eye infections (conjunctivitis, blepharitis, keratitis). At dental practice uses a 2.5% suspension of 0.5-1.0 ml every 4-6 hours.

### *AMPHOTERICIN B*

It has a wide spectrum of action: Candida spp., Cryptococcus, most filamentous and dimorphic fungi. Dermatomycetes are resistant. The only polyene antibiotic for intravenous administration.

*Pharmacokinetics*. Practically not absorbed in the gastrointestinal tract. Penetrates into many organs and tissues, poorly passes through the BBB. T1 / 2 is 24-48 hours, but with systematic use it can increase up to 15 days, due to cumulation in the tissues. It is excreted by the kidneys.

*Indications*. Severe forms of systemic mycoses. It can be applied topically with resistance to other antimycotics. 3% are used in dental practice cream or ointment. The substance of amphotericin B for intravenous administration is not compatible with electrolyte solutions.

*Contraindications*. Violations of the liver, kidneys; diabetes; anemia; agranulocytosis.

*Unwanted reactions*. Often: nephrotoxic reactions; fever, chills, myalgia with the introduction of the drug; allergic reactions. Less commonly, hypotension, neuro- and hematotoxic reactions; phlebitis.

### *LIPOSOMAL AMPHOTERICIN B*

It is a dosage form based on lipid carriers. Amphotericin B built into liposome membranesintact in relation to normal tissues and is released only upon contact with a fungal cell. Its main advantage is its good tolerability. The spectrum of activity is identical to that of conventional amphotericin B. Higher doses may be used.

### *AZOLES GROUP DRUGS*

The group of azoles is represented by topical preparations (clotrimazole, miconazole, econazole, ketoconazole, etc.) and systemic use (ketoconazole, fluconazole, itraconazole). Preparations for topical use do not have fundamental differences from each other.

*Pharmacodynamics.* The mechanism of action is associated with the blockade of the conversion of lanosterol to ergosterol.

***CLOTRIMAZOLE***

*Broad spectrum of antifungal activity.* The activity against fungi of the genus Candida is of primary importance. In dentistry, it is used topically as a 1% solution or cream.

*Unwanted reactions*. Erythema, burning, itching, perioral dermatitis, folliculitis.

*Indications*. Dermatomycosis, candidiasis of the skin, oral cavity, pharynx, vulvovaginal candidiasis.

***MICONAZOLE***

The spectrum of activity is comparable to clotrimazole. In dentistry, it is used in the form of 2% gel (preferred for candidal leukoplakia and chronic mucocutaneous candidiasis), 2% topical liquid or alcohol solution.

***KETOCONAZOL***

Active against Candida spp., dermatophytes, dimorphic fungi.

*Pharmacokinetics*. Well absorbed in the gastrointestinal tract, bioavailability - 75%. Poorly passes through the BBB. It is excreted mainly through the gastrointestinal tract. $T_{1/2}$ - 6-10 hours.

*Indications*. Dermatomycosis, onychomycosis, superficial candidiasis. Not used for invasive mycoses. In dentistry, it can be applied topically as a 2% cream.

*Unwanted reactions*. Dyspeptic disorders, disorders of the liver, endocrine system, neurotoxicity when taken orally.

*Drug interactions*. Inhibitor of microsomal liver enzymes.

Increases the concentration in the blood of cyclosporine, glucocorticoids, indirect anticoagulants.

*Features of use in various categories of patients*. Penetrates through the placental barrier when taken orally. Do not use in case of impaired liver function.

***FLUCONAZOL***

Compared to other azoles, it is better tolerated. Active against fungi of the genus Candida (except C.krusei and C.glabrata), cryptococcus, dimorphic fungi.

*Pharmacokinetics*. Completely absorbed in the gastrointestinal tract. *Bioavailability* (80%) does not depend on food intake. It penetrates well into various

tissues, passes through the BBB. It is excreted mainly by the kidneys. T1 / 2 - 30 hours, increases with renal failure.

*Indications*. Invasive and superficial candidiasis (except cases caused by C.krusei and C.glabrata). Cryptococcosis, ringworm.

*Unwanted reactions*. Dyspeptic disorders; increased activity of transaminases.

*Drug interactions*. Increases the concentration of glipizide, cyclosporine, theophylline, indirect anticoagulants.

*Features of clinical use in various categories of patients*. At older people and with reduced kidney function, cumulation is possible (dose adjustment is required).

***ITRACONAZOL***

Wider *spectrum of activity* compared to fluconazole. Activity against aspergillus and some other filamentous fungi is important.

*Pharmacokinetics*. Well absorbed in the gastrointestinal tract. Bioavailability is higher when taken with food (more than 80%). It penetrates well into the epidermis, nail plates, lungs, liver, skin, bones, etc. Does not penetrate the BBB. Metabolized in the liver, excreted mainly through the gastrointestinal tract. T1 / 2 - 30-45 hours, does not change with renal failure.

*Indications*. Systemic aspergillosis, sporotrichosis, candidiasis (superficial and systemic), superficial mycoses, some other types of fungal infection.

*Unwanted reactions*. Dyspeptic disorders, headaches, water electrolyte disturbances (hypokalemia, edema), arterial hypertension.

*Drug interactions*. Inhibits microsomal liver enzymes (cytochrome P450), increases the concentration of indirect anticoagulants in the blood, oral hypoglycemic drugs, cyclosporine, digoxin, etc.

**Table 26.15. Drug interactions between ketoconazole and itraconazole**

| Preparations | Effect |
|---|---|
| Antacids, anticholinergics, $H_2$-blockers and proton pump inhibitors | impair absorption and reduce the concentration of drugs in the blood |
| cisapride, terfenadine, hypoglycemic drugs | The risk of developing fatal arrhythmias, increased toxic effect |
| Cyclosporine, warfarin. corticosteroids, digoxin, phenytoin | Ketoconazole and promotes drug concentrations in the blood |
| Isoniazid, theophylline, rifampicin | Reduce plasma drug levels |
| Oral contraceptives | Decrease in reliability |

*Features of clinical use in various categories of patients*. Monitoring of liver function and electrolyte balance is necessary (in patients with heart failure).

## DRUGS OF THE ALLILAMINE GROUP

Includes naftifine (for topical use) and terbinafine, used both topically and orally. Active against dermatophytes, fungi of the genus Candida and a number of other fungi.

### *TERBINAFIN*

*Pharmacokinetics*. Well absorbed in the gastrointestinal tract, bioavailability 70%. High concentrations in the epidermis and nail plate. Metabolized in the liver, excreted by the kidneys. $T_{1/2}$ - 17 hours

*Indications*. Onychomycosis, dermatomycosis, superficial candidiasis.

*Unwanted reactions*. Dyspeptic disorders, change in taste. Epidermal necrolysis (rare).

*Drug interactions*. Chloramphenicol can increase, and rifampicin and phenobarbital can reduce the concentration of terbinafine in the blood.

**Table 26.16. Names and dosages of the main antifungal drugs**

| Generic title | Trade title | Doses |
|---|---|---|
| Nystatin | Nystatin | *inside*<br>Adults: 500,000–1 million units every 6 hours within 7–14 days; with oral candidiasis and pharynx dissolve 1 tab. every 6-8 hours after meal.<br>Children: 125–250 thousand units every 6 hours for 7–14 days.<br>*locally*<br>The ointment is applied to the affected areas of the skin 2 times a day. |
| Amphotericin B | Amphotericin B Fungizone | *IV*<br>Adults and children: test dose 1 mg in 20 ml of 5% solution glucose for 1 hour; therapeutic dose 0.3–1.5 mg/kg/day<br>Rules for the introduction of a therapeutic dose: diluted in 400 ml of 5% glucose solution, administered at a |

| | | |
|---|---|---|
| | | rate 0.2–0.4 mg/kg/h.<br>*locally*<br>The ointment is applied to the affected areas of the skin 1-2 times a day. |
| Clotrimazole | Kanesten, Lotrimin | Cream and solution are applied to the affected areas skin with light rubbing 2-3 times a day.<br>With candidiasis of the oral cavity and pharynx -treat the affected areas with 1 ml of solution 4 times a day. |
| Miconazole | Daktarin, Lanaderm | The cream is applied to the affected areas 2 times a day. day. With candidiasis of the oral cavity - gel 1/2 dosing spoon (in 1 spoon - 124 mg miconazole) 4 times a day. |
| Fluconazole | Diflucan, Mycosist | *inside*<br>Adults: 0.1-0.6 g / day in 1 dose; doses and duration depends on the type of infection.<br>Children: with candidiasis of the skin and mucous membranes shells - 1-2 mg / kg / day in 1 dose; at systemic candidiasis and cryptococcosis - 6–12 mg / kg / day in 1 dose.<br>*IV*<br>Adults: 0.1-0.6 g / day in 1 injection.<br>Children: with candidiasis of the skin and mucous membranes shells - 1-2 mg / kg / day in 1 injection; at systemic candidiasis and cryptococcosis - 6–12mg / kg / day in 1 administration. In/in administered by slow infusion at a rate of not more than 10 ml/min. |
| Itraconazole | Kanazol, Orungal | Adults 0.1-0.6 g every 12-24 hours, dose and the duration of the course depends on the type of infection. |
| Terbinafine | Lamisil, Terbizil | *inside*<br>Adults: 0.25 g / day in 1 dose.<br>Children over 2 years old: body weight up to 20 kg - 62.5 mg/day |

| | | |
|---|---|---|
| | | 20-40 kg - 0.125 g / day, more than 40 kg - 0.25 g / day, in 1 dose.<br>*locally*<br>Cream or spray applied to the affected skin areas 1-2 times a day for 1-2 weeks |

## Control questions

1. The drug of choice for empirical therapy of phlegmon of the cellular spaces of the neck:

a) metronidazole
b) gentamicin
c) penicillin
d) amoxicillin/clavulanate
e) co-trimoxazole

2. The causative agent of the furuncle of the facial area is:

a) H.influenzae
b) E.coli
c) B.fragilis
d) S.aureus
e) M.catarhalis

3. Which conclusion is correct regarding the treatment of actinomycosis:

a) penicillin b is the drug of choice.
b) fluconazole is the drug of choice.
c) duration of therapy is 2 months
d) alternative therapy is gentamicin
e) if allergic to penicillins, macrolides are prescribed

4. For the prevention of endocarditis in dental practice, the following is used:

a) ciprofloxacin
b) erythromycin
c) oxacillin
d) metronidazole
e) amoxicillin

5. Which of the following drugs are antiherpetic:

a) acyclovir
b) zanamivir
c) famciclovir
d) lamivudine
e) valaciclovir

6. For the basic regimen for the prevention of parenteral HIV infection, a combination is used:

a) zidovudine + lamivudine
b) lamivudine + ifavirenz
c) ritonavir + amprenavir
d) nelfinavir + indinavir

7. Azolams include:

a) natamycin
b) terbinafine
c) fluconazole
d) nystatin
e) caspofungin

8. As a systemic drug is used:

a) griseofulvin
b) clotrimazole

c) fluconazole
d) miconazole
e) nystatin

9. A risk factor for oral candidiasis is not:

a) use of broad-spectrum antibiotics
b) diabetes
c) cytostatics
d) acetylsalicylic acid
e) corticosteroids

10. For local treatment of oral candidiasis is not applied:

a) nystatin
b) amphotericin B
c) natamycin
d) clotrimazole
e) caspofungin

# Chapter 27 Antiseptics and Disinfectants

## Indications for use in dentistry

The high urgency of the problem of the effectiveness of disinfection and sterilization in dentistry is obvious given the fact that among patients there may be patients with various infectious diseases, virus and bacteria carriers. When carrying out manipulations, there is a real danger of infection of patients and medical staff with HIV infection, hepatitis, herpes, pathogenic microorganisms. A large number of microorganisms settle on surfaces in working rooms, which are sprayed in the form of an aerosol with drops of blood, saliva, sawdust of hard dental tissues when the drill is operating at a distance of about a meter. For the treatment of patients, instruments are used that have a complex configuration that makes their processing difficult. The risk of nosocomial infections in these conditions increases. The number of purulent-inflammatory complications even after "clean" operations is about 30%. All this increases the requirements for modern products used as antiseptics and disinfectants.

## Definition of pharmacological group

In the daily practice of a dentist, much attention is paid to asepsis - to prevent the entry of microorganisms into the wound, tissues, organs, body cavities of the patient during therapeutic and diagnostic manipulations. This is achieved through preventive measures (washing hands, using disposable tools, gloves), the use of modern disinfectants and antiseptics. Unlike asepsis, antiseptic is a set of measures to destroy microorganisms in a wound, tissue, etc.

*Disinfectants* - antimicrobial drugs that do not have selective action, used to prevent the spread of infection, which is achieved by disinfecting medical instruments, devices, utensils, rooms, discharges of patients.

*Antiseptics* - similar products used, usually externally, although some may be used to decontaminate the gastrointestinal tract, urinary system, washing cavities.

Disinfection of multiple medical devices consists of several stages: disinfection, pre-sterilization cleaning and sterilization.

*Disinfection* is a physical or chemical process that kills almost all microorganisms except bacterial spores. In this case, it is possible not to completely destroy microorganisms, but to reduce their number to a level that is safe for the body.

*Pre-sterilization cleaning* is the mechanical removal of foreign, primarily organic material from a disinfected surface.

*Sterilization* is the complete destruction of all microorganisms, including bacterial spores.

Antiseptics that are used to kill microorganisms and disinfectants are called *biocides.*

Biocides must meet a number of requirements. They should act not only on bacteria and fungi, but also be active against spores, hepatitis and human immunodeficiency viruses, Mycobacterium tuberculosis. It is important that the drug exposure is as short as possible.

The antiseptic should not have a local irritant effect, minimal allergenic and toxic properties, minimally absorbed from the site of its application.

The disinfectant should not cause corrosion of metals and damage other materials that are part of medical equipment, remain active in the presence of organic substances (blood, mucus, urine, etc.), not have a toxic and allergenic effect on medical personnel, and be easily washed with treated surface, not to have an irritating effect and odor. In addition, the disinfectant should be easy to use, dissolve well in water, have a long shelf life, and be environmentally friendly and inexpensive.

According to these requirements, the range of chemical compounds that can be used in dental practice as antiseptics and disinfectants, very limited. Each of these compounds has its own advantages and disadvantages.

In the process of using biocides, many microorganisms can develop resistance to certain antiseptics and disinfectants. Different microorganisms have different sensitivity to biocides (Fig. 27.1).

Fig. 27.1. Comparative resistance of microorganisms to antiseptic and disinfectants (According to Russel A.D., Furr J.R., Maillard J.J., 1997).

*Standardization of antiseptics*. Differences in the speed and completeness of action of different antiseptics require their standardization by comparison with a substance that has "reference" antiseptic activity. Phenol is such a substance. Historically, phenol, or carbolic acid, is the prototype of all antiseptics. The possibility of its use for disinfection was discovered in 1865 by the great English surgeon J. Lister, who discovered that preoperative treatment of the surgeon's hands, instruments, and patient's skin with phenol sharply reduces the frequency of postoperative infections. The phenol coefficient of any antiseptic is found by dividing the reciprocal of its minimum effective concentration by the reciprocal of the minimum effective concentration of phenol, moreover, both quantities are determined under the same conditions and in relation to the same microorganisms.

Although the phenol coefficient sets the main standard, there are still many problems in assessing the effectiveness of antiseptics. For example, a substance may be highly active against microorganisms, but toxic to living tissues. Or it destroys bacteria in the external environment, but is relatively inactive in the body.

Currently, among the various groups of antiseptics, agents of high, medium and low levels of activity are distinguished (Table 27.1).

**Table 27.1. The level of activity of antiseptics and disinfectants depending on the impact on various microorganisms. (After Favero N.S., Bond W.W., 1991).**

| Activity level | "cid" effect | | | | | |
|---|---|---|---|---|---|---|
| | bacteria | | | Mushrooms[1] | Viruses | |
| | controversy | Mycobacteria | Vegetative forms | | With shell | Without shell |
| High | +[2] | + | + | + | | + |
| Average | -[3] | + | + | + | +_[4] | + |
| Short | - | - | + | ± | | + |

[1] Including most disputes.

[2] With prolonged exposure and high concentration of disinfectant and a small amount of spores.

[3] Some moderately active disinfectants, such as hypochlorites, may have some sporicidal activity, while most, such as alcohols and phenols, are not active against spores.

[4]Some moderately active disinfectants show some activity at high concentrations and with prolonged exposure.

High-level antiseptics and disinfectants include, for example, aldehydes (formaldehyde, glutaraldehyde, succinic dialdehyde), oxygen-containing drugs (hydrogen peroxide, potassium permanganate). They have pronounced antimicrobial properties against all vegetative microorganisms and some spores. Their disinfecting effect is achieved with short-term exposure (10-45min). Among the means of the middle level, halogens (iodine, chlorine and other drugs), alcohols, phenol and its derivatives (thymol, triclosan, phenol). Low-level substances include, in particular, surface-active compounds: quaternary ammonium compounds (benzalkonium chloride, cetylpyridinium chloride), biguanides(chlorhexidine bigluconate).

**Classification.**

Traditionally, antiseptics and disinfectants are divided according to their chemical structure into organic and inorganic compounds, which can be divided into several main groups:

1. Aldehydes and aldehyde-containing.
2. Oxygen-containing or oxidizing agents.
3.Halogens and halogenatedie.
4. Alcohols.
5. Surface-active substances (surfactants).
6. Phenol and its derivatives.
7. Dyes.
8.Metal salts
9. Acids

In addition to the above division, antiseptics and disinfectants are divided in their own intended purpose (sterilization of surfaces, instruments, treatment of the skin of the hands, mucous membranes, etc.).

**Aldehydes**

The group of aldehydes or aldehyde-containing substances includes formaldehyde, glutaral (glutaraldehyde), succinic dialdehyde, etc. All of them are high level disinfectants.

*Indications* for use in dentistry: disinfection of dental equipment, such as handpieces; aldehydes are included in some filling materials (resorcinol-formalin paste).

*Mechanism of action*. The effect on all types of microorganisms is due to the alkylation of carboxyl, amino and sulfhydryl groups of amino acids and the suppression of protein synthesis in this way.

*Pharmacodynamics*. In practice, deodorant, disinfectant and sterilizing effects of aldehydes. Their bactericidal virucidal, fungicidal properties provide a wide range of activity against bacteria, fungi, viruses, mycobacteria. Among the drugs of this group, glutaral has the highest antimicrobial activity. With regard to spores, aqueous solutions of aldehydes have low efficiency, which increases at pH 7.5-8.5,

**Combinations of aldehyde with alcohol.**

The positive qualities of this group of drugs are the absence or low corrosive activity against metals and the absence of pungent odors(except formalin). Their disadvantages are high toxicity (see below), which requires working with them in the absence of patients, and a pronounced ability to fix organic contaminants - blood, mucus, pus, etc., which requires preliminary washing of medical devices using cotton-gauze swabs or using their combination with surfactants.

*Pharmacokinetics*. Absorption through the skin and mucous membranes is possible. Solutions are stable for 14 days.

*Unwanted actions*. Local: pronounced irritant effect on the skin and mucous membranes of the eyes, nose; strong smell; formaldehyde vapors cause irritation of the respiratory tract, coughing, dysphagia, spasm and swelling of the larynx, bronchitis and pneumonia, in rare cases - pulmonary edema; may have a carcinogenic effect; if ingested - a clinical picture of a chemical burn of the digestive tract (vomiting blood, thirst, toxic shock). Systemic: dyspeptic phenomena, CNS damage (psychomotor agitation, headache, sleep disturbances, visual disturbances, ataxia, convulsions, loss of consciousness), metabolic acidosis, toxic hepato- and nephropathy, renal failure.

*Drug interactions*. Aqueous solutions are medium-level disinfectants, but under optimal conditions - pH 7.5-8.5 or in combination with alcohols (ethyl, isopropyl) their disinfectant activity increases to high-level disinfectants, i.e. pronounced antimicrobial properties are acquired in relation to all vegetative microorganisms and some spores. Thus, bactericidal 2% glutaral solution enhanced with 70% isopropanol (isopropyl alcohol) solution, while being carried out for 10 minutes; the death of spores occurs within 3-10 hours. Aqueous solutions of formaldehyde (1-10%) have a bactericidal effect within 6 to 1 hour, and alcohol - after 15-20 minutes.

**Drugs**

*Formaldehyde* (formaldehyde solution) is used in concentrations of 1-10%, causing the death of microorganisms and spores within 1-6 hours. Aqueous solutions of formaldehyde(0.5-1%), used for a long time to disinfect hands, are now rarely used, as they have a pronounced irritant effect on the skin and mucous membranes, and also due to a sharp specific odor. It is mainly used for disinfection of instruments. More commonly used is a 37% formaldehyde solution with the addition of methyl alcohol, the so-called "formalin", which is used to sterilize the tips.

Formalin is used in the preparation of resorcinol-formalin mixtures and pastes, which are used for disinfection and filling of hard-to-pass tooth canals (according to the method of Albrecht, 1912). At present, the use of the resorcinol-formalin method is abandoned, since relapses of endodontic pathology occur in the long-term period after treatment, there is a significant difficulty in the retreatment of canals, teeth, discoloration of the crown of the tooth, its sharpness and fragility. In addition, there are data on the systemic distribution of the drug in the human body.

*Glutaral* (Glutaral-N, Decones Dental, Erigid Forte, ADS-521) is used as 2% solution for sterilization of dental and other instruments, some prosthetic materials.

Produced in a two-component system (2% solution in jars and bottles of 1-30 liters and powder consisting of activator - alkaline agents, corrosion inhibitor, indicator or dye in film packs of 10 and 300G); in the form of liquid concentrate and liquid concentrate mixed with HOURS.

*Succinic acid dialdehyde* (gigasept FF) is not inferior to glutaral in antimicrobial activity, but is less toxic. The combination with dimethoxytetrahydrofuran enhances the disinfecting properties of succinic dialdehyde and leads to high efficiency in the sterilization of medical devices.

Produced in the form of 11% liquid concentrate with 3% dimethoxytetrahydrofuran in bottles, canisters, barrels of 2, 5 and 200 liters.

Aldehydes also include *methenamine* (hexamethylenetetramine, urotropine), used to treat inflammatory diseases of the urinary tract.

**Oxygen-containing drugs**

*Oxygen-containing substances* (oxidizing agents) include - hydrogen peroxide, potassium permanganate.

*Indications for use in dentistry*. Hydrogen peroxide is used for disinfection and pre-sterilization treatment of dental equipment (mirrors, tips for saliva ejectors, vacuum cleaners, etc.), root canal treatment; in the form of a 3% solution, it is used for washing wounds, rinsing the mouth and also ensuring hemostasis. Aqueous solutions of potassium permanganate (0.1-0.5%) are used as an antiseptic for washing wounds and rinsing the mouth.

*Mechanism of action.* Oxygen-containing drugs are strong oxidizing agents. As a result of the release of atomic oxygen, the formation of free radicals is activated, which leads to damage to the cell membrane and DNA of the microbial cell.

*Pharmacodynamics*: The advantage of this group of drugs is a good cleansing ability, safety, environmental friendliness. Oxygen-containingsubstances have a wide spectrum of antimicrobial activity against bacteria,mycobacteria, fungi, viruses, bacterial spores. Their solutions are odorless.

When hydrogen peroxide comes into contact with damaged skin or mucous membranes, under the influence of catalase, molecular oxygen is released, while mechanical purification and inactivation of organic substances (proteins, blood, pus) occurs.

Of great importance in this case is the mechanical cleansing of damaged tissues.

The antiseptic effect is not sterilizing; when using hydrogen peroxide, only a temporary decrease in the number of microorganisms occurs. Abundant foaming promotes thrombosis and stops bleeding from small vessels. Potassium permanganate, in the presence of organic substances, splits off atomic oxygen, the antiseptic effect of which is more pronounced than molecular oxygen. Atomic oxygen provides an antimicrobial and deodorizing effect, and the forming manganese oxide has an astringent effect. For the deodorizing effect, 0.01-0.1% solutions are used. Solutions of potassium permanganate in dilution 1:10000 cause the death of many microorganisms within 1 hour.

*Pharmacokinetics*. Possible absorption from the surface of the skin and mucous membranes shells.

*Unwanted actions*. In high concentrations, oxygen-containing substances have an irritating and cauterizing effect. With frequent use, a decrease in the sensitivity of microflora, contamination of working solutions was noted.

Hydrogen peroxide (6%) can cause corrosion of some metals and discoloration of treated tissues, and have a resorptive effect. Solutions are unstable during storage, especially in the light and at pH>10 or pH<4.

*Drug interactions*. In the presence of cyanides, azides, sulfites, the activity of oxygen-containing substances decreases. The action of hydrogen peroxide is enhanced in the presence of phenols, iron, copper, manganese, ascorbic acid. When potassium permangant interacts with organic (coal, sugar, tannin) and easily oxidized substances, an explosion may occur.

Catalase insufficiency and acatalasia: are hereditary diseases that manifest themselves in adolescence with recurrent ulceration of the gums. In more severe cases, alveolar gangrene, gum atrophy, and tooth loss occur. The malignant form is characterized by the spread of gangrene to soft tissues and jaw bones. Asymptomatic cases have also been described. In such patients, the use of hydrogen peroxide is not accompanied by the release of oxygen bubbles, and the color of the blood becomes brown-black. People with hypocatalasia and especially those with acatalasia are highly sensitive to alcohol due to the reduced rate of oxidation of ethanol. There is no specific treatment for acatalasia. In the presence of inflammatory foci, antibiotics, sulfonamides, antiseptics, etc. are used.

**Drugs**

*Hydrogen peroxide* (hydrogen peroxide, hydrogen peroxide solution, concentrated hydrogen peroxide solution - perhydrol) is used in the form of a 3% aqueous solution for disinfection and deodorization of the skin, mucous membranes, wounds; 0.25-1% rinse solution for stomatitis; 3% - for pre-sterilization treatment of dental equipment (mirrors, tips, tips for saliva ejectors, vacuum cleaners, etc.)

Produced in the form of 3%, 7.5-11% and 33% solutions in vials, bottles, canisters according to 25, 40, 50, 90, 100, 1000 ml, 10, 20 kg.

*Potassium permanganate* is used in the form of a 0.01-0.1% aqueous solution as an antiseptic for washing wounds and rinsing the mouth, with ulcerative necrotic gingivitis and stomatitis to accelerate the rejection of necrotic tissues. With catarrhal inflammation of the oral mucosa and during the period of epithelialization of erosive and ulcerative surfaces, the drug is not used, as it can damage newly formed epithelial cells. At a dilution of 1:10,000, it causes the death of many microorganisms within 1 hour.

Produced in the form of a powder in bags, jars, test tubes, bottles of 1, 3, 5, 15 g.

**Halogens and halogenated compounds**

The group of halogens and halogen-containing drugs includes substances that have in its structure, fluorine, chlorine, bromine, iodine are often combined with oxygen. They are strong oxidizing agents, have a rapid bactericidal effect. As a result of the rapid release of halogen (in some cases, oxygen) from inorganic compounds, a damaging effect develops not only on microorganisms, but also on tissues.

For a long time, elemental iodine preparations have been used in medicine (iodine solution in alcohol, iodine solution in an aqueous solution of potassium iodide - Lugol's solution). Later they began to use organic iodine- and fluorine-containing compounds that do not damage tissues.

The activity and aggressiveness of halogens decrease with increasing molecular weight: fluorochlorine bromine iodine.

**Chlorine compounds**

*Chlorine compounds* (bleach, chloramine, sodium hypochlorite) are traditional disinfectants used inour country in any industry, although they have already been abandoned all over the world. These agents are toxic, adversely affect living tissues, destroy materials, and are a source of the formation of dioxins, an extremely dangerous class of toxic compounds.

*In dentistry*, they are used both as antiseptics and as disinfectants.

*Mechanism of action*: when chlorine compounds are dissolved in water, hypochlorous acid is formed, followed by the release of free chlorine and active oxygen, which cause denaturation of proteins and nucleic acids, and also suppress some enzymatic reactions in the microbial cell.

*Pharmacodynamics*. Chloroactive compounds have bactericidal, virucidal, fungicidal, and in high concentrations and sporicidal action; disinfectant effect.

*Pharmacokinetics*. Absorption from the surface of the skin and mucous membranes is possible.

*Undesirable effects*: pungent odor, irritation of the mucous membranes of the eyes and upper respiratory tract; discolor painted products, cause corrosion of metals.

*Drug and other interactions*: inactivated by organic substances.

**Drugs**

*Bleach* is not currently used in clinical practice due to poor solubility, poor solution stability, mucosal irritation, metal corrosion, and tissue discoloration.

*Chloramine* (chloramine B) contains 25-29% active chlorine. It is used in the form of soluble tablets. It has a bactericidal effect against gram (+) cocci, less active against gram (-) bacteria, spores and viruses, does not destroy Entamoeba histolytica cysts. It is used for processing premises, non-metallic tools, hands personnel (0.5% solution), root canals (4-5% solution), cavities (0.1% solution), treatment of infected wounds (1.5-2% solution).

Stable when stored dry. Working solutions can be used for 15 days.

*Sodium hypochlorite* (parkan, chlorox) is used in the form of a 0.5-3% solution. Can be used to clean and disinfect contaminated wounds. Hypochlorite, when in contact with tissue proteins, quickly decomposes, releasing atomic chlorine, which combines with amino groups to form chloramine. As a result of chemical reactions occurring with proteins, peptide bonds are broken, proteins dissolve, and do not coagulate, therefore hypochlorite has, in addition to the usual disinfectant, unique property to dissolve the organic contents of the root canals: necrotic tissue, pus, decay products or scraps of extirpated pulp.

**Iodine compounds**

*In dentistry*, elemental iodine preparations are used (iodine solution in alcohol etc.) and organic iodine compounds, which are a reservoir of constantly released molecular iodine (iodinol, etc.)

*The mechanism of action* is associated with the release of iodine, which interacts with amino acids and fatty acids of microbes. Iodine solution in a ratio of 1: 20,000 causes the death of microorganisms within 1 min, and spores within 15 min.

*The antimicrobial effect* of organic iodine compounds is manifested only upon contact with tissues and microorganisms that reduce bound iodine to elemental iodine.

*Pharmacodynamics*. Antiseptic action is achieved due to antibacterial, antiviral and fungicidal effects; local irritant, anti-inflammatory and analgesic effects are also used; preparations of elemental iodine in high concentrations cause a cauterizing effect.

*Pharmacokinetics*. Upon contact with the skin and mucous membranes, 30% of iodine is converted into iodides, and the rest into the active form. Absorption from the surface of the skin and mucous membranes is possible. Absorbed, iodine penetrates into tissues and organs, selectively accumulating in the thyroid gland. Iodine is involved in the synthesis of thyroxine, affects lipid metabolism, reduces blood clotting. It is excreted from the body by the kidneys, partly by the intestines, sweat and mammary glands.

*Unwanted actions*. Local: irritant effect; high concentrations can cause denaturation of proteins at the treatment site, staining of surfaces.

Systemic: iodism - rhinitis, urticaria, angioedema, cough, lacrimation, salivation, nausea, vomiting, headache, acne-like rash; toxic damage to the thyroid gland. Individuals with increased individual sensitivity to iodine may develop dermatitis.

Organic iodine compounds are less toxic.

*Drug interactions*. Pharmaceutically incompatible with essential oils, ammonia solutions. Alkaline or acidic environment, the presence of fat, pus, blood reduces the antiseptic activity of iodine.

*Contraindications*: Hypersensitivity, age up to 5 years. Not recommended from 3 months pregnancy and during breastfeeding. Severe diseases of the liver and kidneys.

**Drugs**

A) Drugs of elemental iodine

*Alcoholic iodine solution* 1%, 2%, 3% is the most common antiseptic for disinfecting intact skin.

*Alcoholic iodine solution* 5% contains elemental iodine (5 parts), potassium iodide (2 parts) water and 95% ethyl alcohol (equally up to 100 parts); It is used as an antiseptic for the treatment of the skin and mucous membranes during surgical interventions.

*Iodine + Potassium iodide + Glycerol* (Lugol's solution with glycerol) contains elemental iodine (1 part), potassium iodide (2 parts), glycerin (94 parts) and water (3 parts), used to treat the mucous membranes of the oral cavity.

B) Organic compounds of iodine

*Iodinol* contains elemental iodine, potassium iodide, polyvinyl alcohol and water. It is used in the form of a 1% solution. A complex compound in which, due to the presence of polyvinyl alcohol, the release of elemental iodine is slowed down, its antiseptic effect is prolonged and the irritating effect on tissues is reduced. It has a bactericidal effect on both gram (+) and gram (-) flora (most active on streptococci and E. coli), as well as pathogenic fungi. Staphylococci are less sensitive. Pseudomonas aeruginosa is stable. It is used for the treatment of root canals, treatment of periodontitis, purulent surgical diseases, thermal and chemical burns.

*Iodonate* is a preparation consisting of 4-5% iodine in combination with a surfactant; contains iodine, potassium iodide, phosphoric acid, emulsifier, water.

It has a high bactericidal activity against many gram (+) and gram (-)microorganisms, spores, has a fungicidal effect. Used as a 1% solution (for which it is diluted with water in a ratio of 1: 4.5) as an antiseptic agent for treating the surgical field during surgical interventions. Use only in a hospital setting. The active solution has a dark brown color, with discoloration of the solution, the antiseptic activity decreases.

*Povidone-iodine* (betadine, iodovidone, octasept, povidone iodine) is a water-soluble complex of polyvinylpyrrolidone and iodine (the concentration of free iodine is 0.1-1%). Used as an antiseptic. Upon contact with the skin and mucous membranes, iodine is gradually and evenly released, providing a local antimicrobial effect against many microorganisms, including Mycobacterium tuberculosis and spores. The effect develops quickly (15-60 sec) and lasts as long as the color remains at the site of application. The osmotic activity of vinylpyrrolidone provides outflow from the wound.
It is produced in various dosage forms: solutions, ointments, aerosols, surgical preparations, shampoos, skin cleansing agents. Povidone-iodine solutions can be contaminated with Pseudomonas and other Gram(-) bacteria. Not compatible with other antiseptics and disinfectants, especially those containing mercury, enzymes, alkalis and oxidizers.

*Povidone-iodine + potassium iodide* (iodopyrone, iodopyrone ointment, sulidopyrone). It is used for the treatment of hands, the surgical field and the treatment of purulent wounds (I phase of the wound process). Produced in the form of a powder for the preparation of solutions(0.1%, 0.5% and 1% solutions are used), ointments, aerosols.

**Alcohols**

*Alcohols* are used in medical practice as antiseptics and disinfectants, both alone and as solvents enhancing the activity of other disinfectants (surfactants) substances, iodine, aldehydes, etc.). In this case, ethyl, propyl and isopropyl alcohols are used. In Russia, ethyl alcohol is more commonly used.

In dentistry, they are used to treat the operating field and the surgeon's hands.

*The mechanism of action* is associated with the denaturation of microbial cell proteins.

*Pharmacodynamics*. Antiseptic and disinfectant; have a bactericidal effect on gram (+) and gram (-) cocci, bacteria, mycobacteria, fungi and viruses. Bacterial spores are resistant, therefore it cannot be used for processing dental instruments. Possible contamination of solutions.

The antibacterial activity of propyl and isopropyl alcohols is higher than that of ethyl alcohol, and the antiviral activity is lower.

*Pharmacokinetics*. Absorption from the surface of the skin and mucous membranes is possible. The optimal concentration is 60-90% alcohol solutions. When processing the skin, 70% ethanol penetrates into the deeper layers of the epidermis than 96%, which has a tanning effect.

*Unwanted actions.* Local: with frequent use - irritation and damage to the skin and mucous membranes(burns).

Systemic: absorbed from treated surfaces, cause CNS depression.

*Drug interactions*. In the presence of water, the activity of alcohols increases; the addition of biocides increases the antiseptic effect by reducing the volatility of alcohols. The combination of alcohol with povidone-iodine enhances the damaging effect (deep chemical burns of the skin are possible), compounds with chlorhexidine - skin necrosis. They fix organic pollution, cause damage to plastic and rubber products.

**Drugs**

*Ethanol* (ethyl alcohol). In Russia, ethanol is predominantly used as an antiseptic. For skin treatment before surgeryn is used in the form of aqueous solutions (40, 70, 90%). In dental practice, an antiseptic, drying and degreasing effect is used (along with ether) when treating a carious cavity in order to ensure better adhesion of a permanent filling material. Abroad, along with ethyl, propyl and isopropyl alcohols (50, 60%) are used.

**Surfactants**

*Surfactants* are divided according to their ability to ionize in aqueous solutions; they are divided into cationic, anionic, ampholytic (amphoteric) and non-ionic. As independent biocides, as the most active, only cationic and ampholytic surfactants are used.

Catonic surfactants include:

- ~ Quaternary ammonium compounds (QAC): cetylpyridinium chloride, benzalkonium chloride, dequalinium chloride, Ethylenedecyloxycarbonylmethyldimethylammonium dichloride, Benzyldimethyl-myristoylamino-propylammonium chloride monohydrate.
- ~ Biguanides: chlorhexidine bigluconate, polyhexamethylene guanidine, alexidine.
- ~ Diamidines: hexamidine, propamidin - are used only in combinations with other drugs.
- ~ Hexahydropyridines: hexetidine.

Ampholan, used in the form of a 2% solution for the treatment of premises, is referred to as ampholytic disinfectants.

**Quaternary ammonium compounds**

*Indications for use:* used for the treatment of premises, furnishings, sanitary equipment, skin of the hands, treatment of purulent wounds, inflammatory diseases of the oral cavity, etc.

*Mechanism of action*: due to a change in the surface tension of water, which helps to cleanse the skin and various objects from fat, foreign particles and microorganisms, i.e. provides a washing effect. In addition, HACs change the permeability of cell membranes, denature proteins and inactivate enzymes.

The preparations are active against vegetative forms of bacteria, fungi and enveloped viruses. However, they do not act on tubercle bacillus, bacterial spores and many viruses.

When applied to the skin, they form a film under which live microorganisms can remain. The disinfecting effect occurs after 0.5-1 hour.

*Pharmacodynamics*: detergent, disinfectant, antiseptic, predominantly fungicidal. Some of them have a local anesthetic effect, stimulate wound healing.

*Pharmacokinetics*. Practically not absorbed.

*Undesirable effects*: allergic reactions in the form of dermatitis, skin itching.

*Drug and other interactions*. The effect of QAC is reduced by surfactants, and therefore they are not compatible with soaps.

Adsorbed by porous and fibrous materials and removed from the solution by such materials.

**Drugs**

*Benzalkonium chloride* (catamine B, incidin liquid, rokkal, pharmatex). It is applied externally in the form of a 1% aqueous solution for primary or primary delayed treatment of wounds, prevention of infection with hospital strains, for the treatment of purulent wounds, drainage of bone cavities in osteomyelitis. room disinfection, furnishings, sanitary equipment and medical products are carried out with 1-12% aqueous solutions. Has a spermicidal effect used as an intravaginal contraceptive (pharmatex). It is used as a preservative in the preparation of many drugs.

*Cetylpyridinium chloride* in dentistry is used in the form of combined preparations: cerigel (cetylpyridinium 0.2 g, polyvinyl butyral 4 g ethanol 96%), for treating the hands of medical personnel before surgical interventions and other manipulations; kalgel (with lidocaine) - for pain during teething in children.

*Dequalinium chloride* (decamine) has an antibacterial effect against gram-positive and gram-negative microorganisms, has antiviral, antifungal, anti-inflammatory, hemostatic action. Used for candidiasis of the oral mucosa; inflammatory processes in the oral cavity and pharynx (tonsillitis, stomatitis, pharyngitis, glossitis,

aphthous stomatitis) sublingually or on the cheek, 0.15-0.3 mg every 3-5 hours, in severe infections - every 2 hours.

*Ethylenedecyloxycarbonylmethyldimethylammonium dichloride (ethonium)* - bisquaternary ammonium compound. It has an antiseptic, analgesic effect and stimulates regeneration processes. Effective against streptococci, staphylococci and other microorganisms. In the form of 0.5-1% ointment, it is used to treat stomatitis, gingivitis, paste - pulpitis, dental caries. In the form of a 1% gel of aethonium on a hydrophilic basis, it is used for chronic recurrent aphthous stomatitis, herpetic lesions, erosive and ulcerative forms of lichen planus and leukoplakia, decubitus ulcers and radiation injuries purulent and gangrenous forms of pulpitis.

*Benzyldimethyl-myristoylamino-propylammonium chloride monohydrate (miramistin)* - 0.01% solution has a bactericidal, fungicidal, virucidal, immunostimulating, wound-healing effect, reduces the resistance of microorganisms to antibiotics. Applytsya for the treatment of purulent wounds in the form of irrigation, in the treatment of periodontitis, hygienic treatment of removable dentures.

**Biguanides**

*Biguanides* are one of the most widely used group of biocides worldwide. In Russia, chlorhexidine is mainly used in the form of gluconate (gebitan) and digluconate and polyhexamethylene guanidine.

*Indications for use*: used for the treatment of premises, medical and sanitary equipment, the operating field and the hands of the surgeon, the treatment of purulent wounds, with purulent-inflammatory diseases of the oral mucosa and periodontium, disinfection of removable dentures, etc.

*Mechanism of action*: due to damage to the cell membrane due to the strongly basic group associated with lipophilic areas, disruption of the ATPase complex and coagulation of the contents of the microbial cell.

*Pharmacodynamics*: detergent, disinfectant, antiseptic.

*Pharmacokinetics*. Practically not absorbed from the surface of the skin. Chlorhexidine after accidental ingestion of 300 mg Cmax is reached after 30 minutes and is 0.206 mcg/l. It is excreted mainly with feces (90%), less than 1% is excreted by the kidneys.

*Undesirable effects*: transient dryness and itching of the skin, dermatitis is possible, allergic reactions.

*Use with caution in children*.

*Drug and other interactions*. The disinfectant effect is enhanced by alcohols. The bactericidal effect increases with increasing temperature. In an acidic environment, the

efficiency drops sharply. The simultaneous use of iodine preparations is not desirable in order to avoid the development of dermatitis.

**Drugs**

*Chlorhexidine* - according to its chemical structure, it can be attributed to chlorine-containing, biguanide QAS derivatives and cationic antiseptics.

Depending on the concentration used, it exhibits both bacteriostatic and bactericidal action against gram-positive and gram-negative bacteria. Bacteriostatic action (both aqueous and alcoholic working solutions) is manifested in a concentration of 0.01% or less; bactericidal – in concentrations of more than 0.01% at a temperature of 22 degrees C and exposure for 1 min. Fungicidal action - at a concentration of 0.05%, a temperature of 22 degrees C and an exposure of 10 minutes.

*Virucidal action* - manifests itself at a concentration of 0.01-1%. Does not affect acid-resistant forms of bacteria, microbial spores, fungi, viruses. Stable, after treatment of the skin (hands, surgical field) remains on it in a certain amount, sufficient to exhibit a bactericidal effect. Retains activity (although somewhat reduced) in the presence of blood, pus, various secrets and organic matter. The systematic use of chlorhexidine leads to the accumulation of this substance on the skin and an increase in the antimicrobial effect.

*In dentistry* for rinsing, irrigation and applications for gingivitis, stomatitis, periodontitis, alveolitis apply 0.05%, 0.2% and 0.5% aqueous solutions. 5-10 ml of the solution is applied to the affected surface of the mucous membranes with an exposure of 1-3 minutes 2-3 times a day. A solution of chlorhexidine gluconate (0.2%) reduces the formation of plaque.n A gel with chlorhexidine 1% (elugel) is also used.

Treatment of medical instruments and work surfaces is carried out with a clean sponge moistened with a 0.5% antiseptic solution, or by soaking. Disinfection of the surgical field is carried out with a 0.5% solution in 70% ethanol for 5 minutes; hand disinfection - 0.5% solution in 70% ethanol or 1% aqueous solution.

Chlorhexidine is produced in the form of finished dosage forms for disinfection and antiseptics (hibiscrab, plivasept, etc.).

*Undesirable effects*: Allergic reactions (skin rash), dry skin, itching, dermatitis, stickiness of the skin of the hands (within 3-5 minutes), photosensitivity.

When using a dental gel or rinse solutions, the color of the teeth, tongue and filling material may change, tartar deposition, desquamation of the oral mucosa and swelling of the salivary glands may occur, taste disorders.

*Sebidin* - a compound of chlorhexidine with ascorbic acid is used to treat gingivitis and other inflammatory diseases of the oral cavity.

Alcoholic solutions (0.5%, 1.5% solutions in 70% ethyl alcohol) are used to treat the surgeon's hands.

*Tsiteal* is a foaming antiseptic solution for external use.

*The composition of the drug includes*: hexamidine (100 mg) - a cationic antiseptic from the group of diamidines, chlorhexidine (20% solution 0.5 ml), chlorocresol (300 mg) - an antiseptic from the group of halophenols. It is used to treat the skin and mucous membranes at a dilution of 1:10, wounds, hands of staff.

*Polyhexamethyleneguanidine (anavidin, polysept)* - has a local antimicrobial, antiviral, antifungal effect, is used as a disinfectant for treating rooms, work surfaces in medical institutions.

**Hexahydropyridines**

The main representative is *hexetidine* (hexoral, stopangin).

*Indications for use*: infectious-inflammatory and fungal diseases of the oral cavity and larynx, tonsillitis, pharyngitis, stomatitis, glossitis, gingivitis, periodontal disease, periodontal disease, alveolitis, aphthae, gum bleeding, trauma and surgery (pre- and postoperative period) of the mouth and larynx, prevention of superinfection; as a hygienic and deodorizing agent for bedridden and needy patients.

*Pharmacodynamics*: broad-spectrum antimicrobial and antiseptic drug for topical use, active against gram-positive and gram-negative microorganisms and fungi.

It is used as a 0.1% solution for rinsing or washing for 30 seconds or applied with a cotton swab to damaged areas; 0.2% solution in the form of a spray treat the affected areas for 1-2 seconds.

*Undesirable effects:* allergic reactions, decreased appetite, impaired taste sensations; with prolonged use - a change in the color of the teeth.

*Contraindications*: hypersensitivity, children under 4 years of age.

**Phenol-containing drugs**

*Phenol* was historically the first antiseptic used in surgical practice in 1867 by Lister. Currently, its use and its derivatives are limited due to an unpleasant pungent odor, irritating and sensitizing effects of some of them, and carcinogenic effects.

Biphenolic derivatives of triclosan and hexachlorophene are used as biocidal additives to soaps, toothpastes, antiseptic creams and ointments.

*Mechanism of action:* Interact with the proteins of the microbial cell, causing their denaturation, disrupt the colloidal state of the cell, dissolving in the lipids of the cell membrane, increase its permeability; affect redox processes.

*Pharmacodynamics*: They have bactericidal activity againstand vegetative forms of bacteria (mainly aerobic) and fungi; it has little effect on spores; has a disinfecting effect. Some have a cauterizing effect.

*Pharmacokinetics*: easily absorbed through the skin and mucous membranes. Soluble in water alcohol, glycerin.

*Adverse reactions*: vomiting, diarrhea, agitation followed by CNS depression, respiratory disorders, pulmonary edema, dysfunction of the heart, liver, kidneys, acidosis, erythrocyte hemolysis, methemoglobinemia, multiple organ failure.

*Drug interactions*: not described. In an acidic environment, the activity is higher.

**Drugs**

*Triclosan* is used in the form of 0.2-0.5% alcohol solutions, is part of some types of toothpastes, soaps.

*Polycresulen* (Vagotil) in dentistry is used as a local antiseptic and cauterizing agent for sluggish healing wounds with granulations, stomatitis, aphthous stomatitis, and hypertrophic gingivitis. With small surgical dental interventions, it can be used for hemostatic purposes.

**Dyes**

Microorganisms vary greatly in their ability to stain with certain dyes and their affinity for some of them. Many dyes turned out to be antiseptics.

The drugs in this group include ethacridine lactate, brilliant green, methylthioninium chloride (methylene blue), which have bacteriostatic, and at high concentrations and bactericidal action. They are used as external antiseptics in the treatment of skin and mucous membranes.

*Mechanism of action*: associated with inhibition of bacterial growth due to affinity for phosphoric acid groups of nucleoproteins.

*Pharmacodynamics*: antiseptic, disinfectant, cauterizing

*Pharmacokinetics*: practically not absorbed from the surface of the skin and mucous membranes; poorly soluble in water and alcohols.

*Adverse reactions*: local allergic reactions.

*Characteristics of individual drugs:*

In dentistry, ethacridine lactate (rivanol) is used. It has an antimicrobial effect, mainly in infections caused by cocci, especially streptococci. At high concentrations, it coagulates proteins, at low concentrations it exhibits a certain selectivity, inhibiting some enzymes of microorganisms. The drug is slightly toxic, does not cause tissue irritation. With inflammation of the mucous membranes of the mouth, pharynx, nose use rinsing with a 0.1% solution or lubrication with a 1% solution.

*Interaction*: Pharmaceutically incompatible with alkalis (forms a precipitate), with sulfates, chlorides, salicylates, benzoates (forms insoluble compounds).

*Contraindications*: Hypersensitivity, albuminuria.

**Metal salts**

In modern dentistry, salts of some heavy metals are used as caustic agents in high concentrations. For this purpose, compounds of silver, copper and, less commonly, zinc are used. The use of this group of agents is limited due to their damaging effect on surrounding tissues.

*Mechanism of action*: cause protein precipitation and irreversibly block sulfhydryl groups of microbial cell enzymes.

*Pharmacodynamics*: cauterizing, sclerosing, antiseptic.

*Pharmacokinetics*: easily absorbed through the skin and mucous membranes; readily soluble in water and alcohol.

*Adverse reactions*: resorptive action, addiction, tissue necrosis.

*Drug interactions*: incompatible with organic substances(decompose), with chlorides, bromides, iodides (precipitate forms). They disintegrate in the world.

**Drugs**

*Silver nitrate* - 3-5% aqueous solutions are used for root canal impregnation in the treatment of periodontitis; for the treatment of mucous membranes, freshly prepared 0.25-2% aqueous solutions. Included in the liquid argenate, intended for antiseptic treatment of infected and impassable canals, carious milk teeth in children and teeth affected by cervical caries.

*Silver sulfadiazine* is a topical sulfonamide preparation. It has a wide spectrum of antibacterial action. Applied in the form 1% ointment.

*Zinc sulfate or chloride* - used for cauterization of 20% aqueous solution. Included in the paste used to sterilize the canals of the tooth (cresont-paste).

*Zinc oxide* is used externally as an astringent and disinfectant for skin diseases.

**Acids**

*Acids* are used as antiseptics in the treatment of lesions caused by pathogenic fungi and bacteria, as a cauterizing agent.

*Mechanism of action*: contribute to a change in the pH of the oral cavity and increase the dissolution of mucus; at certain concentrations cause protein denaturation, inhibition of enzymes necessary for the vital activity of microorganisms.

*Pharmacodynamics*: deodorizing, antiseptic.

*Pharmacokinetics*: absorbed through the skin and mucous membranes, especially in young children, slowly excreted from the body and may accumulate in organs and tissues.

*Adverse reactions*: primarily local irritant, cauterizing.

*Ingestion*: boric acid: nausea, vomiting, diarrhea, skin rashes, epithelial desquamation, headache, confusion, convulsions, oliguria; in rare cases - shock conditions.

**Drugs**

In dentistry, boric acid and its derivative sodium tetraborate are used.

*Boric acid,* by coagulating the proteins of a microbial cell, breaks the permeability of its membrane. It is used in the form of 1-3% alcohol solution as a deodorant. Currently rarely used due to toxic effects on the body. In some countries excluded from the Register of medicines.

*Sodium tetraborate* has bacteriostatic activity. It removes the mycelium of the fungus from the mucous membranes, disrupts the process of attaching the fungus to the mucous membranes and inhibits its reproduction (it is not an antifungal drug, because it does not have a fungicidal or fungistatic effect). In dentistry, it is used for candidal lesions of oral mucosa in the form of a 20% solution in glycerin.

## Control questions

1. Which statement regarding disinfection is correct:

a) Disinfection is the complete destruction of all microorganisms, including bacterial spores.
b) Disinfection is a physical or chemical process that kills almost all microorganisms except bacterial spores.
c) Disinfection is the mechanical removal of microorganisms from the wound surface.
d) Disinfection is the immunoprophylaxis of the population.
e) Disinfection is the isolation of infectious patients.

2. High-level disinfectants include:

a) 10% formalin solution
b) 3% boric acid solution
c) 1% water solution brilliant green
d) 1% water solution methylene blue
e) 1% benzalkonium chloride solution

3. Which statement regarding formaldehyde is incorrect:

a) The bactericidal effect develops after 10 hours.
b) The bactericidal effect develops after 15 minutes.
c) The bactericidal effect develops instantly.
d) The bactericidal effect develops after 1 hour.
e) The bactericidal effect develops after 30 minutes.

4. Which statement regarding aldehydes is incorrect:

a) The combination of aldehyde with alcohol increases disinfectant activity.
b) The combination of aldehyde with alcohol reduces disinfectant activity.
c) The combination of aldehyde with water reduces the disinfectant activity.
d) The combination of aldehyde with alcohol is a stable compound.
e) Aldehydes irritate mucous membranes.

5. Which statement regarding hydrogen peroxide is correct:

a) Frequent use of hydrogen peroxide leads to a decrease in disinfectant properties.
b) Frequent use of hydrogen peroxide leads to an increase in disinfectant properties.
c) Frequent use of hydrogen peroxide does not affect the disinfectant properties.
d) Hydrogen peroxide is a low level disinfectant. E. Hydrogen peroxide does not corrode metals.

6. For the treatment of root canals use:

a) 5% solution of bleach.
b) 5% solution of chloramine.
c) 0.5% solution of chloramine.
d) 1% benzalkonium chloride solution
e) Lugol solution

7. For disinfection of root canals, you can use:

a) Hydrogen peroxide.
b) Chloramine 5% solution
c) 1% solution of sodium hypochlorite.
d) Formaldehyde.
e) 1% solution of benzalkonium chloride

8. Organic iodine compounds are used for:

a) For root canal treatment.
b) For unsealing root canals.
c) For processing tips.
d) For cleaning premises
e) For soaking tools.

9. For the treatment of inflammatory diseases of the oral cavity, use:

a) 1.5% chlorhexidine solution.
b) Compound of chlorhexidine with ascorbic acid.
c) 4% chlorhexidine solution.
d) 50% isopropyl alcohol
e) Formaldehyde

10. To treat the hands of a dentist, you can use:

a) 3% solution of hydrogen peroxide.
b) Formaldehyde
c) Cresol
d) 10% bleach solution
e) 0.5% chlorhexidine solution.

# Chapter 28 Vitamins

***Vitamins*** are indispensable food organic low molecular weight compounds, present in the body in small amounts and necessary for the performance of normal cellular functions. Most vitamins are coenzymes or their precursors. In addition, there are so-called vitamin-like substances (for example, vitamin P or vitamin B15), whose functions are not as specific as those of vitamins, but which are usually considered together with the latter.

**Indications for use in dentistry**:

Doses corresponding to the daily requirement (prophylactic) can only be used to prevent the development of deficient conditions;

Pharmacological doses are used:

- ~ for the treatment of deficient conditions and their manifestations in the oral cavity;
- ~ in the treatment of inflammatory, hyperkeratic, erosive and ulcerative lesions of the mucous membranes, periodontal diseases and hard tissues of the tooth, cracks, burns, consequences of injuries, as well as in the postoperative period to accelerate the healing process.

**Classification of vitamins**. Allocate fat- and water-soluble vitamins (Table 28.1). They differ in pharmacokinetic properties, the possibility of developing hypervitaminosis and some other properties.

**Table 28.1. Vitamin classification**

| Fat soluble | Water soluble |
|---|---|
| **Vitamin A** - the combined name of the group retinoids - retinol (vitamin $A_1$), 3-dehydroretinol (vitamin $A_2$), retinal and retinoic acid.<br>**Vitamin D** - a group of structurally related hormone-like substances(secosteroids), of which the most important for humans - ergocalciferol (vitamin $D_2$) and cholecalciferol (vitamin $D_3$).<br>**Vitamin E** is a group of tocopherols, the largest the activity of which has - α- | **Vitamin C** (ascorbicnew acid).<br>**Vitamin P** is a group of flavonoids, among which to natural substances include rutin and quercetin, and derivatives - rutoside (venoruton) and troxerutin (troxevasin).<br>**Vitamin $B_1$**(thiamine).<br>**Vitamin $B_2$**(riboflavin).<br>**Vitamin $B_3$ or PP** (nicotine acid = niacin, nicotinamide = niacinamide).<br>**Vitamin $B_5$** (pantothenic acid).<br>**Vitamin $B_6$** (pyridoxine). |

| | |
|---|---|
| tocopherol.<br>**Vitamin K** is a group of naphthoquinone derivatives, of which phytylmenaquinone (vitamin $K_1$) comes from food, and multiprenylmenequinone (vitamin $K_2$) is synthesized by the intestinal microflora. | **Vitamin $B_8$ or H** (biotin).<br>**Vitamin $B_9$** or Sun (folic acid).<br>**Vitamin $B_{12}$** (cyanocobalamin).<br>**Vitamin $B_{15}$** (pangamic acid). |

**The physiological significance of vitamins, hypo- and avitaminosis**.

Vitamins enter the body with food. Some of them (for example, K, B12, folic acid) in small amounts can be synthesized by the intestinal microflora.

There are also provitamins (for example, carotenoids), from which active vitamins are formed in the body (retinides - vitamin A). The lack of vitamins can lead to the development of a specific syndrome of vitamin deficiency - hypo- and avitaminosis. Allocate subclinical and clinical stages of vitamin deficiency.

It is believed that against the background of subclinical vitamin deficiency, the incidence of infectious diseases increases. In addition, it is combined with many chronic diseases. Since vitamins interact closely in the process of metabolism, as a rule, develops a deficiency of several vitamins at once.

Manifestations of the clinical stage of vitamin deficiency are shown in the table 28.2.

**Table 28.2. Manifestations of vitamin deficiency**

| **Vitamin** | **Clinical symptoms** | |
|---|---|---|
| | **dental** | **others** |
| A (retinol) | Xerostomia, enhanced keratinization up to the formation of papillomas; increased traumatization epithelium, infection, ulcerative stomatitis. | hemeralopia, xerophthalmia, keratomalacia. Dull Rare hair, cross striation and brittle nails, dryness, pallor and peeling of the skin. Poor wound healing. Decline resistance to infections. Growth slowdown, decline appetite, weight |

| | | |
|---|---|---|
| | | loss. Decrease formation of steroids, thyroxine, goiter development. |
| D (ergocalciferol, cholecalciferol) | Violation of the structure of the teeth, caries, osteoporosis alveolar bone. | Rickets in children, osteoporosis, osteomalacia in adults |
| E (tocopherol) deficiency syndrome expressed indistinctly. | Gingivitis: high gums susceptible to deficiency vitamin E. | Muscle dystrophy, hair loss, pregnancy complications. |
| K (phylloquinones) In adults rare | Bleeding gums. | Gastrointestinal bleeding, intradermal and subcutaneous hemorrhages. |
| C (ascorbic acid) Expressed deficiency manifests itself scurvy. | Swelling and bleeding gums, loosening of teeth, petechiae on OM, ulcerative gingivitis, stomatitis. | Weakness, fatigue, pain in muscles, pain in the legs, in particular, feet, hemorrhages in the skin, subcutaneous tissue, joints, internal organs, etc. Dryness skin, bleeding of mucous membranes. Decreased immunity. bad wound healing, recurrent infections. Fever. Violation bone formation. Anemia. Achlorhydria. |
| B1 (thiamine) Expressed vitamin deficiency appears take take | ? | Decreased appetite, general weakness, weight loss, neurosis, irritability, poor sleep, lethargy, heightened fatigue. Peripheral neuritis, paresthesia, atrophy muscles, cramps. Tachycardia, heart failure. Pain in epigatria, vomiting, flatulence, |

| | | |
|---|---|---|
| | | constipation. |
| $B_2$ (riboflavin) | angular stomatitis, glossit, "magenta" language. | Seborrheic hyperkeratosis, dermatitis in the genital area. Vascularization of the corneaconjunctivitis, photophobia, lacrimation. Paresthesia. Growth retardation. Anemia. Congenital alformations. |
| A nicotinic acid ($AT_3$) Expressed deficiency manifests itself pellagra | Stomatitis, glossitis | Dermatitis, pigmentation of open skin areas, loss of appetite, diarrhea, dystrophic changes brain and spinal cord, fat and protein disorders exchange. |
| Pantothenic acid ($B_5$) | Glossitis. | Dermatitis, dizziness, headaches, weakness, insomnia, paresthesia, nausea, vomiting, flatulence, disturbance functions of the sex glands. |
| B6 (pyridoxine) | ? | Protein metabolism disorders, synthesis GABA, epinephrine, norepinephrine, dopamine, histamine, microcytic sideroahrestic anemia. |
| $AT_{12}$ (cyanocobalamin) The deficit caused absence internal factor Kasla leads to pernicious Addison's anemia Birmera | Glossitis, stomatitis. | Megaloblastic anemia (hyperchromia and macrocytosis erythrocytes) in combination with leuko- and thrombocytopenia, enteritis, demyelination of nerve fibers |

| | | |
|---|---|---|
| Folic acid (Sun, $B_9$) | -----“----------“----- | Megaloblastic anemia (hyperchromia and macrocytosis erythrocytes) in combination with leuko- and thrombocytopenia, enteritis. |
| Biotin (B8) | ? | Seborrheic dermatitis, atony bowel, anorexia, paresthesia. |

Depending on the causes, vitamin deficiency can be divided into *primary* and *secondary*.

*Primary vitamin deficiency* occurs due to inadequate diet at:

- ~ prolonged malnutrition;
- ~ an unbalanced diet with a predominance of carbohydrates, a deficiency or excess of protein (an increase in the calorie content of food increases the need for vitamins; when eating carbohydrate-rich foods, the need for vitamin B1 increases, and with a lack of protein, the absorption of vitamin B2, nicotinic and ascorbic acids decreases; with an increase in food content protein of plant origin increases the need for nicotinic acid);
- ~ artificial feeding from the first days of life;
- ~ lack of vitamins in mother's milk.

*Secondary vitamin deficiency* is the result of:

- ~ violations of absorption in diseases of the gastrointestinal tract, biliary tract, pancreas, taking drugs that negatively affect the absorption of vitamins, for example, laxatives, oral contraceptives;
- ~ transport disorders (hypoproteinemia);
- ~ violations of the metabolism of vitamins (and, accordingly, a violation of their absorption) due to for genetic disorders of enzyme systems, their age-related inferiority,
- ~ diseases of the liver, kidneys, endocrine system, smoking, alcoholism or taking drugs that disrupt their metabolism (for example, oral contraceptives disrupt the metabolism of pyridoxine, and alcohol, methotrexate, trimethoprim - folates, anticonvulsants - vitamin D, folates; insufficient sun exposure - vitamin D );
- ~ increased consumption (pregnancy, lactation, periods of growth and puberty, feverish conditions, physical and psycho-emotional stress, high or low air temperature, hypoxia, taking chemotherapeutic agents);

- ~ one of the causes of a secondary deficiency of water-soluble vitamins may be an excess intake of fat-soluble vitamins.
- ~ in hypo- and avitaminosis, the appointment of vitamins has a rapid clinical effect. Given the diverse effects of vitamins on metabolic processes, they are widely used in a variety of diseases, but in many of them the effectiveness of vitamins has not been firmly proven. Most water-soluble vitamins are not stored in the body, and their excess is quickly excreted. To achieve a clinical effect that is not associated with the prevention or treatment of deficiency, vitamins should be used for a long time in maximum (pharmacological) doses, significantly exceeding their daily requirement. In this case, it is possible not only to obtain a therapeutic effect, but also the appearance of side effects that are not characteristic of small doses.

Irrational nutrition or the presence of factors that can cause secondary vitamin deficiency make it necessary to prescribe vitamins in prophylactic doses (physiological daily doses) in the form of appropriate preparations.

*Side effects*. When prescribed in doses corresponding to physiological needs, vitamins do not have side effects, with the exception of allergic reactions, the development of which, as already indicated, does not depend on the size of the resolving dose. Most of the complications of vitamin therapy are the result of an overdose and the development of toxic effects.

**Characteristics of individual vitamins**

*Vitamin A* is the combined name for a group of retinoids (see table. 28.1), each of which performs certain functions (see below).

*Mechanism of action and pharmacodynamics*. Retinoids in the form of a retinoid-retinol-binding protein complex interact with the corresponding receptors on the celloh membrane, penetrate into the cell nucleus and regulate protein synthesis, included in a number of enzymes, thus participating in the formation of:

- ~ components of connective tissue, cartilage, bones and the main intercellular substance,
- ~ liver enzymes,
- ~ heparin,
- ~ taurine (which is involved in synaptic transmission, stimulates the synthesis of growth hormone, has an anti-calcium effect, and is also part of taurocholic bile acid),

~ somatomedins (produced under the influence of growth hormone and necessary for the formation of proteins, nucleic acids, collagen, as well as inhibitors of lipolysis).

*Retinol*, being a glycation cofactor of polypeptide chains, is involved in ensuring the completion of phagocytosis, in cell adhesion and intercellular interaction.

It is necessary for the growth and differentiation of tissues, especially epithelial, reproduction.

*Retinoic acid* is also important for the growth and differentiation of the epithelium (participates in the synthesis of epithelial cell enzymes) and prevents its premature keratinization. It activates receptors for calcitriol (an active metabolite of vitamin D).

Retinal is necessary for the synthesis of visual pigments, in particular rhodopsin, which ensures the normal function of the retina, including twilight vision.

In conditions of vitamin A deficiency, the division of immunocompetent cells is disrupted, synthesis of immunoglobulins and other factors of specific and nonspecific protection, including secretory immunoglobulin A, lysozyme, providing local protection of oral mucosa.

***Pharmacokinetics.***

*Absorption*. Fat-soluble vitamin A enters the gastrointestinal tract dissolved in fats. Inside it is prescribed in the form of oil solutions of retinol esters and acetic or palmitic acids. Under the action of hydralases of the pancreas and the intestinal mucosa, free retinol is released, which enters the cells of the intestinal epithelium, where it is again converted into palmitic acid ester and enters the bloodstream. For the absorption of the vitamin, bile and food containing oils are needed.

*The bioavailability* of vitamin A is about 12%. In newborns up to 6 months, the activity of hydralases is low, and a significant part of the retinol supplied with food is not absorbed. When administered intramuscularly, only retinol acetate is absorbed.

*Distribution and association with proteins.* Non-protein bound vitamin A is toxic. In blood retinol binds to lipoproteins. It is actively taken up by the liver, where it is deposited in the form of palmitic acid ester (95–96%) and in the free state (4–5%). Vitamin depot is considered to be sufficient if it in a newborn exceeds 20 mcg / g of liver tissue, and in an adult - 270 mcg / g. Subsequently, as a result of hydrolysis, free retinol is released from the ether, which is transported using a special carrier - retinol-binding protein (RBP). The retinoid-RSB complex enters the bloodstream, where it binds to another protein, transteritin. The high molecular weight of the resulting complex (76000) prevents the loss of the vitamin through the kidneys; it enters the tissue as needed. A decrease in the plasma level of vitamin A less than 100 μg/l

indicates hypovitaminosis. For liver diseases, toxicosis of pregnant women hydrolysis of retinol ester in hepatocytes is disturbed, which can lead to hypovitaminosis even with sufficient hepatic depot. In addition to impaired liver function, the synthesis of RBP decreases with a deficiency of zinc and vitamin A. With nephropathy, the permeability of the renal epithelium for protein molecules increases and RBP is lost in the urine.

Vitamin A enters the fetus through the placenta and is deposited in the liver. Its reserves in a full-term baby are enough for 2-3 months. The concentration of retinol in breast milk is about 500 mcg / l, which, when consuming 750 ml of mother's milk, provides the child with up to 375 mcg of retinol.

*Metabolism and elimination*. Vitamin A is metabolized in the liver. Inactive metabolites are excreted by the kidneys, intestines, and lungs. A small part of the active drug is reabsorbed (enterohepatic circulation).

*Elimination* of vitamin A is slow: about 34% of the dose received is excreted in 21 days. Slow excretion serves as the basis for its cumulation.

Part of the retinol is oxidized to retinoic acid, which occurs mainly in the skin, where there is a special binding protein. In plasma, the concentration of retinoic acid is 150 times lower than that of retinol; it is not deposited in the liver and is excreted by the kidneys.

*Overdose.* Hypervitaminosis develops with prolonged intake of doses exceeding the daily requirement. This disrupts the normal functioning of cellular and subcellular membranes, activates lipid peroxidation, increases the synthesis of heparin; organs and tissues are damaged. The secretion of cerebrospinal fluid increases and intracranial pressure increases. Patients complain of headache, dizziness, drowsiness, lethargy. Nausea, vomiting, other symptoms of meningism, subfebrile fever, arterial hypotension, tachycardia, visual disturbances, liver function (jaundice, hypoproteininemia). Fatty degeneration of the liver develops; hyperazotemia, hemorrhagic syndrome. Due to the increased activity of osteoclasts, bone tissue resorption occurs, hypercalcemia, pain and swelling along the bones appear. Dryness and peeling of the skin, dryness and brittle hair are noted.

For the treatment of hypervitaminosis, glucocorticoids are prescribed, which accelerate the biotransformation of retinol and stabilize cell membranes. Reducing intracranial pressure is achieved by the introduction of mannitol.

*Drug interactions*. A decrease in the absorption of vitamin A in the gastrointestinal tract is observed when it is taken simultaneously with nitrites, cholestyramine, activated charcoal, antacids. Not compatible with tetracycline antibiotics.

Vitamin E enhances the absorption of retinol in the intestine, slows down its metabolism, contributes to the preservation in the active form and increase the concentration of vitamin A in blood.

Salicylates and corticosteroids reduce the risk of side effects.

*Contraindications:*

- ~ hypersensitivity to the drug,
- ~ I trimester of pregnancy
- ~ chronic pancreatitis,
- ~ cholelithiasis.

*With extreme caution*, vitamin A should be used in patients at risk and at the same time carefully monitor the condition of patients.

Retinoids in doses exceeding physiological ones disrupt the normal development of the fetus, therefore, in the II and III trimesters of pregnancy, taking vitamin A and nutritional supplements containing it, we allow only on the recommendation of a doctor. The teratogenic effect persists for a long time after the course of treatment, as a result of which it is recommended to plan a pregnancy 6–12 months after its completion.

In patients with kidney disease, severe heart failure, the metabolism and elimination of the vitamin are disturbed, which requires dose adjustment and careful monitoring of the development of side effects.

When applied topically in the oral cavity, part of the drug is swallowed, and systemic effects may develop.

*Prescription and dosage.* With beriberi of mild and moderate severity, the dose for adults is 33000 IU / day, for children over 7 years old 5000 IU / day, up to a year - 2500 IU every other day, from a year to 7 years - 2500 IU / day inside; with hemeralopia,nxerophthalmia, retinitis pigmentosa, adults are prescribed up to 50,000–100,000 IU / day, children - 1000-5000 IU / day; for skin lesions in adults - 50,000–100,000 IU / day, children - 5000-10000-20000 IU / day. Oil solutions of vitamin and vegetable oils, containing carotene are applied topically, lubricating the mucous membrane 5-6 times a day.

Available in dragee (acetate or palmitate) 3300 IU, coated tablets (acetate or palmitate) 33000 IU, capsules 3300, 5000, 33000, 100000 IU, oil solution (acetate or palmitate) at 30,000, 100,000, 250,000 IU / ml in vials and dark glass dropper bottles of 10, 15, 30, 50 ml, and in the form of an oil solution(acetate) at 25,000, 50,000 and 100,000 IU / ml (ampoules).

***Vitamin D*** - the combined name of the group of calciferols (see table. 1), with anti-rachitic activity. Ergocalciferol (vitamin D2) and colecalciferol (vitamin D3), which are important for humans, are formed during ultraviolet irradiation of the skin: the first is from ergosterol (found in terrestrial plants, seaweed, phyto- and zooplankton and enters the human body with food, including fish), the second - from 7-dehydrocholesterol. This process is influenced by the season, time of day, skin

pigmentation (for the synthesis of an equal amount of the vitamin, black skin requires 10 times longer exposure than white skin).

*Mechanism of action and pharmacodynamics*. The most important physiological function of vitamin D is to stimulate intestinal absorption of calcium and phosphate and influence the accumulation of these ions in the bones.

After interacting with specific intracellular receptors, the active metabolites of vitamins D2 and D3 penetrate into the cell nucleus, where they activate the synthesis of specific and nonspecific proteins involved in the process of calcium and phosphorus metabolism. Vitamin D is needed for:

- ~ transport of calcium and phosphates through the cells of the intestinal mucosa and renal tubules, as well as the capture of calcium from the blood and its deposition in growth zones (participation in the synthesis of specific proteins and alkaline phosphatases, the effect on the composition and function of cell membranes);
- ~ binding excess calcium in the cells of the intestinal mucosa and protecting them from its damaging effect (participation in the synthesis of specific proteins);
- ~ ossification (participation in the synthesis of osteocalcinin, which serves as a matrix for ossification);
- ~ collagen synthesis, in which calcium phosphorus salts are deposited;
- ~ maintaining normal levels of calcium and phosphate in the blood: in case of hypocalcemia, calcitriol activates not only the absorption of calcium from the intestine, but also bone resorption; in case of hypocalcemia and hypophosphatemia, bone calcification stops (that is, the effect of vitamin D depends on adequate supply of calcium and phosphorus).

Vitamin D also:

- ~ increases the reabsorption of sodium, amino acids, citrates, carnitine;
- ~ activates the processes of differentiationVKI and proliferation of chondrocytes and osteoblasts of bones;
- ~ breaks down phospholipids that prevent the mineralization of the organic matrix of the bone (by activating the phospholipase of osteoblasts and chondrocytes);
- ~ takes part in the synthesis of thyroid-stimulating hormone, interleukin1, inhibits the production of gamma globulins, interleukin2, increases the phagocytic activity of macrophages, activates differentiation and inhibits the proliferation of undifferentiated cells.

**Pharmacokinetics.**

*Absorption*. Vitamin D is absorbed from the gastrointestinal tract in the distal small intestine. Its bioavailability, usually 60–90%, depends on the presence of fat and bile in the intestine, and in their deficiency can be reduced to zero. The bioavailability of synthetic water-soluble vitamin D2 preparations is not affected by bile and fats. Compared to fat-soluble forms, water-soluble forms are absorbed 5 times faster, at the same time, 7 times more drug is deposited in the liver.

*Distribution and association with proteins*. Vitamin D circulates in the blood bound to alpha-globulin, which protects it from inactivation in the liver and from excretion in the urine. It is distributed to the myocardium, adipose tissue, kidneys, adrenal glands, adipose tissue, liver,skeletal muscles, in which up to 20% of the vitamin is deposited. Most of the vitamin (80%) is deposited in the liver, from where, as needed, it enters the blood in the form of calcidiol, where it binds to a carrier protein.

Calcidiol crosses the placenta well; ergocalciferol and calcitriol are somewhat worse. Vitamin D is excreted in breast milk.

*Metabolism and elimination*. In the liver, an inactive form of the vitamin, calcidiol, is formed, which enters the kidneys, where it is transformed into the active form, calcitriol. This process is regulated by growth hormone, vitamins C, E, B2.

In violation of the function of the liver and kidneys, the metabolism of vitamin D suffers and its hypovitaminosis develops. In these cases, synthetic vitamin preparations are prescribed that do not require activation in the body.

Within 24–48 hours, 1–2% of an administered dose of vitamin D is excreted in the urine, and 30% is excreted in the urine, bile, partially being reabsorbed in the intestine. The elimination half-life is 18–31 days; Vitamin D is stored for a particularly long time in adipose tissue. With repeated administration, cumulation is noted. The half-life of synthetic drugs is much shorter, for example, calcitriol - 10-12 hours.

*Overdose*. Hypervitaminosis is manifested by hypercalcemia, activation of the formation of free radicals, damage to cell membranes, impaired transport of calcium and magnesium into the cell, and a decrease in their intracellular content. The released intracellular enzymes damage the tissues of the internal organs, in particular the liver and kidneys. Hypercalcemia leads to calcification of blood vessels, heart valves. Arterial hypertension, cardiac arrhythmias appear, the contractile function of the myocardium is disturbed. Characterized by abdominal pain, diarrhea, polyuria, thirst. Possible subfebrile condition, convulsions. According to the severity of the clinical picture, there are 3 stages of hypervitaminosis D

**Table 28.3. Clinical picture of hypervitaminosis D**

| Stage | Degree gravity | Clinical symptoms |
|---|---|---|
| I | Light | Decreased appetite, sweating, irritability, sleep disturbance, delayed weight gain, calciuria. |
| II | Medium | Anorexia, occasional vomiting, weight loss, hypercalcemia, hypophosphatemia, hypercytremia, hypomagnesemia. |
| III | Heavy | Vomiting, significant weight loss, myocardial dystrophy, pancreatitis, pneumonia, nephropathy, other changes, biochemical indicators; multi-organ system develops failure. |

Regular monitoring of calcium and phosphate levels in the blood plasma or calcium in the urine can help prevent the development of hypervitaminosis.

Treatment of hypervitaminosis begins with the abolition of vitamin D and the appointment of vaseline oil to stop its absorption in the intestine. Glucocorticosteroids and phenobarbital, vitamins A, E C are prescribed. Symptomatic anticalcium therapy is carried out with verapamil, magnesium, potassium and furosemide, regular intake of which increases the excretion of calcium.

The use of an inhibitor of osteoclastic bone resorption of ksidifon, a domestic drug that prevents calcium deposition in soft tissues, is shown inhibiting the formation of calcitriol, which stabilizes phospholipid complexes of cell membranes.

*Drug interactions*. Vitamins A, E, C, B2, B1, B6, pantothenic acid prevent the development of hypervitaminosis and contribute to the therapeutic effect of vitamin D.

Phenobarbital and anticonvulsants, such as carbamazepine (Finlepsin), phenytoin (difenin) and others speed up the metabolism of vitamin D.

Thiazide diuretics increase the risk of hypercalcemia.

Glucocorticoids reduce the activation of calcium absorption in the intestine.

When administered together with cardiac glycosides, the risk of glycoside intoxication increases.

*Contraindications*:

- ~ hypersensitivity to the drug,
- ~ hypercalcemia, hypercalcemiaciuria,
- ~ active forms of tuberculosis, sarcoidosis,
- ~ urolithiasis with calcium stones,
- ~ peptic ulcer of the stomach and duodenum,
- ~ acute and chronic liver diseases,
- ~ organic heart disease
- ~ pregnancy, lactation.

With extreme caution, vitamin D should be used in patients at risk:

- ~ in case of impaired renal function, it is necessary to monitor the content of calcium in the blood.
- ~ in children, especially those who are artificially fed, the risk of overdose is increased.

*Appointment and dosage*. For the prevention of hypovitaminosis in children under one year old, 400-500 IU / day are prescribed under the supervision of a doctor (dose adjustment depending on the infant formula used, season, etc.) Therapeutic dose is 5000 IU / day under the control of calcium levels in the blood and urine.

For caries in children 6–8 years old, 5 drops of a 0.25% oil solution are prescribed during meals 2 times a day, for a month. Prophylactic dose - up to 100 IU / day for several months.

Available in dragee (acetate or palmitate) 3300 IU, coated tablets (acetate or palmitate) 33000 IU, capsules 3300, 5000, 33000, 100000 IU, oil solution (acetate or palmitate) at 30,000, 100,000, 250,000 IU / ml in vials anddark glass dropper bottles of 10, 15, 30, 50 ml, and in the form of an oil solution(acetate) at 25,000, 50,000 and 100,000 IU / ml (ampoules). Calcitriol - 0.25 mcg / day.

***Vitamin E*** - includes 8 tocopherols, of which α-tocopherol has the highest biological activity and is used as a medicine.

Dosage forms of vitamin E are esters of acetic (acetate) or succinic (succinate) acid.

*Mechanism of action and pharmacological effects*. Vitamin E is a component of biological membranes, forming complexes with selenium and polyunsaturated fatty acids, mainly arachidonic ones. Possessing a pronounced antioxidant activity, it inhibits the formation of lipid peroxides in cell membranes, thereby maintaining their integrity and functional activity. In addition, it prevents the oxidation of prostaglandin precursors with the formation of endoperoxides, thereby affecting the processes of platelet aggregation and controlling the synthesis of prostaglandin E2 in the brain tissue.

Vitamin E regulates the expression of genes responsible for the synthesis of mucosal proteins, collagen of the subcutaneous tissue and bones, contractile proteins of skeletal and smooth muscles, myocardium, placental proteins, liver enzyme proteins, creatine phosphokinase, enzymes involved in the synthesis and destruction of gonadotropic hormones.

Vitamin E activates the synthesis of heme and hemoglobin, myoglobin, catalases, peroxidases, tissue respiration enzymes - coenzyme Q and cytochromes, including cytochrome P450. It controls not only energy (formation of energy in mitochondria), but also synthetic processes in tissues.

***Pharmacokinetics.***

*Absorption*. When taken orally, vitamin E esters undergo hydrolysis under the influence of enzymes in the intestinal mucosa. Tocopherol is absorbed in the middle part of the small intestine. To absorb vitamin E, you need a sufficient amount of bile and fat. In violation of the blood supply and / or bowel function, with cholestasis, the absorption of vitamin E is impaired, which leads to its deficiency.

*Distribution and association with proteins*. The transport of tocopherol to tissues is carried out with the participation of very low density beta-lipoproteins. Its main part is deposited in adipose tissue, muscles, liver. The content of vitamin E in the blood does not reflect its true quantity in the body. When administered intramuscularly, it undergoes hydrolysis in the blood and tissues and passes into the active form.

Tocopherol does not cross the placenta well.

*Metabolism and excretion*. It is metabolized in the liver to form several quinone metabolites, some of which also have vitamin activity. It is excreted mainly with bile into the intestinal lumen, where it is partially reabsorbed. Water-soluble metabolites are excreted in the urine. Vitamin E is slowly excreted from the body. So, 80% of parenterally administered tocopherol is excreted in the bile in 1 week.

*Overdose*. Hypervitaminosis is manifested by the suppression of phagocytosis due to excessive inhibition of free radical reactions in phagocytes, which contributes to the development of infections.

Tocopherol has a direct toxic effect on neutrophils, platelets, intestinal epithelium, liver and kidney cells.

When using large doses, epigastric pain, diarrhea, creatinuria, decrease in performance.

*Side effects*. With intramuscular injection, swelling, redness, and soft tissue calcification at the injection site are possible.

*Drug interactions*. Combined use with vitamins A, D increases efficiency and prevents toxic effects.

*Contraindications*:hypersensitivity to the drug.

*With extreme caution*, vitamin E should be used in patients at risk - with an increased risk of developing thromboembolism.

*Prescription and dosage*. Application - with periodontitis inside and / m 200 - 300 mg / day, locally 30% oil solution on turundas in periodontal pockets for 7-10 minutes. after curettage, within 5 - 6 days. With erosive and ulcerative lesions of the oral mucosa, applications of a 10% solution 2-3 times a day, for 10 days, often in combination with vitamin A.

Available in dragee (acetate or palmitate) 3300 IU, coated tablets (acetate or palmitate) 33000 IU, capsules 3300, 5000, 33000, 100000 IU, oil solution (acetate or palmitate) at 30,000, 100,000, 250,000 IU / ml in vials and dark glass dropper bottles of 10, 15, 30, 50 ml, and in the form of an oil solution (acetate) at 25,000, 50,000 and 100,000 IU / ml (ampoules).

**Vitamin C - ascorbic acid.**

*Mechanism of action and pharmacodynamic effects*. Vitamin C, together with its metabolite, dehydroascorbic acid, forms a redox system that transports a hydrogen ion. Ascorbic acid is involved in

- ~ the formation of active metabolites of vitamin D (that is, it is its synergist),
- ~ synthesis of collagen, hyaluronic acid, steroid hormones, naradrenaline, carnitine,
- ~ absorption of iron from the intestine and its incorporation into heme,
- ~ activation of metal enzymes,
- ~ redox processes,
- ~ antioxidant protection (the antioxidant effect is manifested only with a sufficient amount of other antioxidants in the body - tocopherol,
- ~ glutathione; with their deficiency or with an excess of ascorbic acid, it acts as a pro-oxidant).

**Pharmacokinetics.**

*Absorption*. When using chewable tablets, ascorbic acid is passively absorbed through the oral mucosa. Active absorption with the participation of glucose occurs in the small intestine and is disturbed during hypoxia, inflammatory bowel diseases. The degree of absorption as the dose increases to 200 mg increases to 70%, decreasing with a further increase in dose. The maximum concentration in the blood is reached after 4 hours after ingestion. Ascorbic acid can be administered intramuscularly and intravenously.

*Distribution and association with proteins*. Ascorbic acid accumulates in platelets, leukocytes, posterior pituitary gland, adrenal glands, ocular epithelium, and liver.

*Does not bind to whey proteins.*

*Metabolism and elimination*. Deoxyascorbic and diketogulonic acids are formed in the liver and, partially, in the kidneys. The latter is converted into oxalic acid. It is excreted by the kidneys unchanged and as oxalic acid.

*Overdose.*Hypervitaminosis is manifested by irritability, anorexia, severe hyperesthesia, shortness of breath, dryness and pallor of the skin, petechiae, follicular hyperkeratosis, keratoconjunctivitis, anemia. With prolonged use of large doses, the exchange of zinc, copper is disturbed, oxaluria appears. Hemorrhagic syndrome develops (decrease in platelet aggregation), hyperglycemia and glucosuria (suppression of insulin secretion, increased release of glucagon, reduced entry of glucose into cells). There is a decrease in capillary permeability and deterioration of tissue trophism, thrombocytosis, hyperprothrombinemia, erythrocytopenia, neutrophilic leukocytosis,

development of microangiopathy, damage to the glomerular apparatus, stone formation in the urinary tract. The excitability of the central nervous system increases, arterial hypertension occurs. Termination of pregnancy (increased estrogen synthesis) is possible, as well as hemolysis and the appearance of Heinz shadows in erythrocytes in newborns (prooxidant action).

Children with acute withdrawal of large doses develop Meller-Barrow syndrome. (clinically manifested by hypovitaminosis).

*Side effects*. When using chewable tablets, damage to the oral mucosa is possible. Dyspepsia. Distortion of the results of laboratory tests (blood glucose, transaminases, bilirubin, LDH).

Drug interactions. Ascorbic acid cannot be administered in the same syringe or in an infusion solution with cyanocobalamin, riboflavin, analgin. It reduces the effect of heparin and indirect anticoagulants. When administered simultaneously with iron preparations, salicylates, penicillins, tetracycline, ethinyl estradiol, their plasma level increases.With simultaneous use with salicylates, the risk of developing crystalluria increases. Oral contraceptives reduce the absorption of ascorbic acid, long-term use of salicylates and corticosteroids depletes its reserves, and tetracyclines, amidopyrine increase its excretion.

*Food and other interactions*. Fresh fruit and vegetable juices, alkaline drinks reduce the absorption of vitamin C. Smoking, drinking alcohol reduce the concentration of ascorbic acid in blood. Ascorbic acid increases the total clearance of ethyl alcohol.

*Contraindications*: hypersensitivity to the drug, for large doses - a tendency to thrombosis, thrombophlebitis, hypercoagulability.

With extreme caution, avoiding large doses, vitamin C should be used in patients at risk: with diabetes, with urolithiasis.

*Prescription and dosage.* The prophylactic dose for adults is 50-100 mg per day orally after meals, for children - 25 mg per day. For the treatment of hypovitaminosis, 100-250 mg per day is prescribed; children 50-100 mg per day. In the treatment of scurvy, the dose reaches 1 g per day in 4 divided doses. Parenterally administered intramuscularly and intravenously, 1-5 ml of a 5-10% solution. The maximum single dose is 0.2 g, the daily dose is 0.5 g. Children are given 1-2 ml of a 5% solution for 2-3 weeks. In case of poisoning, the dose can reach 60 ml per day.

Produced in dragees of 0.05 g, tablets of 0.025, 0.05, 0.1, 0.25, 0.5, 2.5 g, tablets for chewing of 0.2 and 0.5 g, effervescent tablets of 0.25, 0.5 and 1 g, 0.5 g capsules, drops for oral administration of 0.1 g / ml, as well as in the form of a powder for the preparation of a solution for oral administration; in the form of a 5% and 10% solution for injection in ampoules of 1, 2 and 5 ml and a lyophilized powder for solution for injection in ampoules of 0.05 mg with solvent.

**Vitamin P** - belongs to the group of flavonoids, the function in the body of both natural substances (rutin and quercetin) and derivatives (rutoside and troxerutin) is closely related to vitamin C.

*Mechanism of action and pharmacodynamics*. Vitamin P provides the transition of ascorbic acidoty into dehydroascorbic acid and prevents further conversion of the latter into inactive diketogulonic acid. It helps to reduce the exudation of the liquid part of the plasma and diapedesis of erythrocytes through the vascular wall.

**Pharmacokinetics.**

*Absorption.* Rutin is absorbed by their gastrointestinal tract worse than rutoside and troxerutin.

*Metabolism and elimination*. Metabolized in the liver, inactive metabolites are excreted through the kidneys. In unchanged form, a small part is excreted in the urine and bile.

*Overdose.* Cases of overdose and hypervitaminosis are not described.

*Side effects*. Unknown.

*Prescription and dosage*. It is prescribed together with vitamin C for increased vascular permeability, extravasation of the liquid part of the plasma, leading to edema of the lower extremities. Produced in the form of a combined preparation - ascorutin - in tablets of 0.05 g ascorbic acid and 0.05 g of rutin.

**Vitamin B1 - thiamine.**

*Mechanism of action and pharmacological effects*. The active form of thiamine - thiamine pyrophosphate (cocarboxylase) acts as a coenzyme for the dehydrogenases of pyruvic and alpha-ketoglutaric acids, supporting the functioning of the tricarboxylic acid cycle (Krebs cycle), the main energy "boiler" of the body.

Thiamine is involved in the synthesis of acetylcholine, fatty acids, steroid hormones, nucleotides, nucleic acids, proteins, in the regulation of the metabolism of carbohydrates, proteins. With its deficiency, metabolic acidosis develops. It has neurotropic activity, participates in the conduction of a nerve impulse, the regulation of the “painful” activity of the nerve.

**Pharmacokinetics**.

*Absorption*. No more than 5–10 mg of thiamine can be absorbed from the intestine per day, due to the fact that this process is carried out by active transport with energy consumption and has “saturation”. In severe hypovitaminosis, the intestinal mucosa contains more free carrier, and the bioavailability of thiamine increases.

*Distribution and association with proteins*. Thiamine penetrates well into tissues, forming a depot in the kidneys, brain, heart, and adrenal glands. Does not bind to whey proteins.

It easily passes through the placenta, in the blood of the fetus its content is higher than in the blood of the mother; thiamine reaches high concentrations in breast milk, and under normal conditions there is no need for additional administration of thiamine to newborns.

*Metabolism and elimination.* In the intestinal wall, and then in the liver, thiamine undergoes phosphorylation, turning into thiamine pyrophosphate. Metabolized to mainly in the liver. Metabolites and unchanged vitamin are excreted through the kidneys. The elimination half-life is 9.5–18.5 days.

A synthetic derivative of thiamine, benfotiamine, is a fat-soluble form of vitamin B1. When it is absorbed, there is no saturation effect. Its bioavailability is 4-5 times, and the maximum concentration in the blood is 6-7 times higher and lasts longer in the blood than when taking thiamine. Thanks to this, benfotiamine provides a better accumulation of the vitamin in cells, and, consequently, greater efficiency.

*Overdose.* With intravenous administration of large doses, synaptoplegia develops - thiamine forms complexes with various mediators that have a ganglion blocking and muscle relaxant effect, which leads to arterial hypotension, arrhythmias, violation of the contraction of skeletal, including respiratory muscles. The introduction of calcium and prozerin preparations produces an insignificant therapeutic effect.

*Side effects*.Increased activity of liver enzymes.

*Drug interactions.* Due to the ability of thiamine to form complex compounds or break down, it should not be mixed in the same syringe or infusion solution with other drugs (for example, lasix, benzylpenicillin, ATP), including vitamins. When combined with thiamine, the excretion of vitamin B2 increases.

*Contraindications:* hypersensitivity to the drug.

*With extreme caution*, vitamin B1 (especially when used parenterally) should be used in patients at risk - with a history of allergic reactions.

*Prescription and dosage*. Inside the dose of thiamine chloride for adults is 10 mg 1-3 times (up to 5 times) in day; duration of admission - 30-40 days. Children under 3 years of age are prescribed 5 mg every other day, from 3 up to 8 years, 15 mg every other day in 3 doses, children over 8 years old - 10 mg 1-3 times a day; duration of admission - 20-30 days.

Inside the dose of benfotiamine for adults is 100-200 mg per day for a period of 15-30 days. Children from 1 to 10 years old - 10-30 mg per day for 1-20 days; children over 10 years old -30–35 mg per day for 15–30 days. Persons of elderly and senile age - 25 mg 1-2 times a day.

Intramuscular dose for adults is usually 25 - 50 mg of thiamine chloride 1ml of 2.5% or 5% solution) or 30-60 mg of thiamine bromide (1 ml of 3.6% solution) per day.

Children are prescribed 12.5 mg of thiamine chloride (0.5 ml of a 2.5% solution) or 15 mg of thiamine bromide (0.5 ml of a 3% solution) per day. The duration of treatment is 10 - 30 days.

*Issued:*thiamine chloride in tablets of 0.005 and 0.01 g, in the form of a 2.5 and 5% solution for injection inampoules of 1 ml;thiamine bromide in the form of 3 and 6% injection solution in 1 ml ampoules;benfotiamine (benfogamma 150, benfotimin) in tablets of 0.005 and 0.025 g and in a dragee of 150 mg.

**Vitamin B2 - riboflavin**.

*Mechanism of action and pharmacodynamic effects*. As part of coenzymes (FMN and FAD) vitamin B2 is involved in the transport of hydrogen ions, providing one of the stages of tissue respiration. It is part of many enzymes (glutathione reductase, xanthine oxidase, etc.), is involved in the activation of pyridoxine and folic acid, formation and inactivation of neurotransmitters. It is needed to convert phenylalanine to catecholamines. It is needed for the absorption of phenylalanine, and with its deficiency, the absorption of this amino acid is impaired; participates in the synthesis of erythropoietins, globin. It is necessary for the normal functioning of avascular (epithelial tissues), the lens and tissues most sensitive to lack of oxygen (the brain). Riboflavin protects the retina from ultraviolet radiation, transforms the short-wavelength blue rays of the light spectrum into longer green ones, to which the retina is more sensitive.

*Pharmacokinetics.*

*Absorption*. It is found in protein-bound form in foods. In the wall of the proximal small intestine, it is released from protein, undergoes phosphorylation, and is absorbed by active transport.

*Distribution and association with proteins*. The largest amounts of vitamin in the body are found in the myocardium, liver, kidneys, and brain. Penetrates through the placenta and into breast milk.

*Metabolism and elimination.* It is excreted by the kidneys unchanged, with excessive intake into the body, its excretion increases, and the urine turns intense yellow.

*Undesirable actions* - hypersensitivity reactions, visual impairment, kidney function, discoloration of urine.

*Drug interactions*. Riboflavin reduces the activity of tetracycline, oxytetracycline, doxycycline, erythromycin and lincomycin; incompatible with streptomycin. Excessive doses of thiamine, thyroid hormones (thyroxine and triiodothyronine), psychotropic drugs (aminazine, imizin, amitriptyline) increase the

excretion of riboflavin. Lack of carotene disrupts its activity. M-anticholinergics increase the absorption of riboflavin.

*Contraindications*:hypersensitivity to the drug., nephrolithiasis.

*With extreme caution* and according to strict indications, vitamin B2 should be used in patients at risk: risk groups are pregnant and lactating women. With hyperthyroidism, the excretion of riboflavin is accelerated.

*Priscription and dosage.* Inside adults 5-10 mg (children 2-5 mg) 1-3 times a day for 1-1.5 months. Intramuscularly for adults 1 ml of 1% solution once a day for 10-15 days(children 3-5 days old), then 2-3 times a week in total - 15-20 injections.

Available in tablets of 0.002 and 0.01 g; as a 1% solution for injection and 1% solution for intramuscular injections in 1 ml ampoules.

Release form - tablets according to., Riboflavin mononucleotide - injection solution in ampoules of 1.0 ml 1% solution.

**Vitamin B3 or PP - nicotinic acid (niacin), nicotinamide(niacinamide).**

*Mechanism of action and pharmacodynamic effects*. Nicotinic acid amide in the form of coenzymes (NAD and NADP) is involved in almost all metabolic processes: in the transport of hydrogen, that is, in glycolysis and cellular respiration, as well as in the synthesis of proteins and fats. Nicotinic acid provides the transition of retinol into the form, going to the synthesis of rhodopsin. It increases the activity of the fibrinolytic system of the blood and reduces platelet aggregation, reduces the synthesis of cholesterol, triglycerides, very low density lipoproteins, increases the level of high density lipoproteins. Under the influence of nicotinic acid, histamine is released and activated kinin system, it takes part in hematopoiesis, stimulating the formation reticulocytes and normocytes.

**Pharmacokinetics.**

*Absorption.* Nicotinic acid and its amide are well absorbed in the pyloric stomach and duodenum by active transport. In diseases of the gastrointestinal tract, the absorption of the vitamin is reduced.

*Metabolism and elimination*. Small amounts of nicotinic acid can be synthesized by the liver and red blood cells from the amino acid tryptophan with the participation of vitamins B2 and B6. Most of the administered dose is excreted unchanged in the urine, a smaller part undergoes hepatic metabolism.

*Overdose*. When administered in large doses, it causes asthenia, a metallic taste in the mouth, anorexia, vomiting, diarrhea, convulsions, hyperglycemia, hyperuricemia, erosion of the gastric mucosa, abnormal liver function, arrhythmias, symptoms of thiamine and riboflavin deficiency; with prolonged use, the development of fatty infiltration of the liver is possible.

*Side effects.* Effects related to histamine release and activation of the kinin system: hypotension, dizziness, pruritus, increased secretion of hydrochloric acid, dysuric symptoms. Taller decreased activity of liver enzymes, impaired liver function. Decreased glucose tolerance. Uricemia.

*Drug interactions.* Nicotinic acid potentiates the action of antispasmodics. It reduces the effectiveness of hypoglycemic agents. When combined with fibrates and statins, the risk of toxic liver damage and rhabdomyolysis increases(although the lipid-lowering effect is increased). Combined use with alcohol and hepatotoxic drugs increases the risk of liver damage. The combination with anticoagulants and fibrinolytics increases the risk of developing hemorrhagic syndrome.

*The bioavailability* of nicotinic acid is reduced when co-administered with cholestyramine, an interval of 1.5–2 hours is required between their doses.

*Contraindications*: hypersensitivity to the drug, peptic ulcer of the stomach and duodenum in the acute stage, severe liver dysfunction, gout, hyperuricemia.

*With extreme caution*, nicotinic acid should be used in patients at risk: with diabetes (it is necessary to control the level of glycemia), with peptic ulcer of the stomach and duodenum in remission, during pregnancy and lactation (as prescribed by a doctor for symptoms of deficiency).

When taking a vitamin, it is necessary to control the level of liver enzymes and blood bilirubin.

*Prescription and dosage.* Inside take after a meal. The prophylactic dose for adults is 15–25 mg per day; for pellagra, 100 mg 2-4 times a day are prescribed, for hyperlipidemia - 2-3 g per day, for other diseases - 20-100 mg per day. For children, the prophylactic dose is 5–20 mg per day; prescribed for pellagra 5-50 mg per day, for other diseases - 5-30 g per day. Parenterally, adults are administered 1 ml of a 10% solution 1-2 times a day.

Available in tablets of 0.005, 0.015, 0.025, 0.05, 0.1 and 0.5 g; as 1, 2.5 and 5% solution for injection in ampoules of 1 and 2 ml.

Release form - tablets 0.05 g, solution for injection in ampoules, 1 ml 10%.

**Vitamin B5 - pantothenic acid (in medical practice it is used in the form of calcium pantothenate).**

*Mechanism of action and pharmacodynamic effects.* It is part of the enzymes necessary for the synthesis of fatty acids, cholesterol, steroids, acetylcholine. Improves the energy supply of the contractile function of the myocardium, accelerates the processes of regeneration. Provides the normal structure of cell membranes, is involved in the transmission of nerve impulses. Pantothenic acid deficiency in humans has not been described.

**Pharmacokinetics.**

*Absorption*. Vitamin B5 is well absorbed from the gastrointestinal tract.

*Metabolism and elimination*. Not metabolized, can be synthesized in the liver from pantoic acid and beta-alanine in the presence of vitamin B6. It is excreted unchanged in the urine (70%) and bile (30%).

*Side effects*. Dyspepsia. Soreness and infiltration at the injection site when administered intramuscularly.

Drug interactions. Enhances the effects of cardiac glycosides, reduces the toxicity of anti-tuberculosis drugs, arsenic.

*Contraindications*: hypersensitivity to the drug, hemophilia, hypokalemia.

*Prescription and dosage.* Applied in the form of a calcium salt of 0.1 - 0.2 g 2 - 4 times a day. Outwardly for lotions and rinses use a 5% solution 2 to 4 times a day.

Available in tablets of 0.1 g; in the form of 10 and 20% solution for injection in ampoules of 2 and 5 ml.

**Vitamin B6 - pyridoxine**.

*Mechanism of action and pharmacodynamic effects*. The active form of vitamin B6 - pyridoxal phosphate provides the reactions of transamination, deamination, amino acid decarboxylation, protein synthesis, in particular siderophilin, transporting iron from the blood to the bone marrow and other tissues; purine and pyrimidine bases that are part of nucleic acids; heme, prostaglandins, coenzyme A. Pyridoxine is involved in the synthesis of dopamine and norepinephrine, the CNS inhibitory mediator - gamma-aminobutyric acid, serotonin, which has an anticonvulsant effect, and nicotinic acid. It is necessary for the active absorption of amino acids and magnesium from the intestines, their transport to the tissues.

**Pharmacokinetics.**

*Absorption*. Well absorbed from the gastrointestinal tract in proportion to the dose.

*Distribution and association with proteins.* Pyridoxine easily penetrates into various organs and tissues, reaching maximum amounts in the muscles and liver; passes through the placenta; the concentration of pyridoxal phosphate in umbilical cord blood is higher than in maternal blood. Does not bind to serum proteins.

*Metabolism and elimination*. It is metabolized in the liver with the formation of active metabolites (the main one is pyridoxal phosphate) and the final inactive metabolite, which is excreted in the urine. Excess pyridoxine is also excreted in the urine unchanged.

*Overdose*. With prolonged (more than 1-1.5 months) use of large doses (more than 200-300 mg per day), drug dependence and toxic polyneuropathy may develop. With rapid on / in the introduction, convulsions are possible.

*Side effects.* Numbness, a feeling of pressure in the limbs - a symptom of "stockings" and "gloves". Increased gastric secretion of hydrochloric acid. Decreased lactation.

*Drug interactions*. Potentiates the action of diuretics, reduces the effect of levodopa. isoniazid, cycloserine, penicillamine reduce the effects of pyridoxine. Incompatible in one syringe and infusion solution with vitamins B1 and B12.

*Contraindications*: hypersensitivity to the drug.

*With extreme caution*, vitamin B6 should be used in patients at risk: with peptic ulcer of the stomach and duodenum, in nursing mothers (threat of lactation suppression), with severe liver damage (large doses can cause a deterioration in its function).

*Prescription and dosage*. Inside take 15 minutes after eating. The prophylactic dose for adults is 2-5 mg per day, for children - 2 mg per day. Therapeutic doses for adults are 20-30 mg 1-2 timesbut per day; For children, the dose is reduced according to age. Parenterally, adults are prescribed 50-100 mg per day; children - 20 mg per day.

Available in tablets of 0.002, 0.005, 0.01 g; in the form of 1, 2.5 and 5% solution for injection in ampoules of 1 and 2 ml.

**Vitamin B12 is cyanocobalamin**.

*Mechanism of action and pharmacodynamic effects*. The active form of vitamin B12, cobamamide, serves as a cofactor for various reducing enzymes. With hypoproteinemia, the synthesis of the protein part of these enzymes is disrupted and enzymatic deficiency develops, even with a sufficient amount of vitamin B12. It is necessary for the conversion of folic acid into an active form necessary for the synthesis of nucleic acids, nucleoproteins, proteins, for cell division, including hematopoietic ones. Participates in the formation of glutathione (prevents hemolysis), succinic acids (part of myelin), methionine (provides methyl groups for the synthesis of various compounds, including acetylcholine).

Vitamin B12 is essential for normal erythropoiesis. It provides myelination of nerve fibers, reduces peripheral pain sensitivity, prevents fatty degeneration of cells and tissues of parenchymatous organs.

**Pharmacokinetics.**

*Absorption.* It comes with food and is synthesized by the intestinal microflora. For the assimilation of the vitamin when it is taken orally, a mucoprotein synthesized by the stomach is needed - the internal factor of Castle, with which cyanocobalamin forms

a complex and enters the intestine. Absorption occurs actively with the participation of transport proteins, which limits the intake of the vitamin due to the "saturation" of this mechanism. When creating non-physiologically high concentrations of the vitamin in the intestine, less effective passive absorption is also possible.

*Distribution and association with proteins*. In the blood, cyanocobalamin binds to proteins - transcobalamins, which deliver it to tissues. The vitamin is stored in the liver. From the liver with bile it enters the intestine, where it is absorbed again (enterohepatic circulation), which maintains its content in the body at a constant level. Through the placenta, the vitamin enters the fetus, where it is also deposited in the liver. Cobamamide penetrates well through the blood-brain barrier.

*Metabolism and elimination*. In the body, vitamin B12 is converted to cobamamide. It is excreted in the urine and through the gastrointestinal tract unchanged.

*Side effects.* Acne. Mental excitement. Headache, dizziness. Cardialgia, tachycardia. When using high doses - hypercoagulability, impaired purine metabolism.

**Drug interactions**. Vitamin B12 is incompatible in one syringe or infusion solution with thiamine, riboflavin, pyridoxine, ascorbic acid, salts of heavy metals. It potentiates the action of blood clotting agents, which can lead to hypercoagulability. Biguanides (metformin, etc.), para-aminosalicylic acid (PAS), high doses of vitamin C reduce the concentration of cyanocobalamin in the blood. High doses of folic acid can cause deficiency vitamin B12 (which is especially dangerous in older age groups). Chloramphenicol (levomycetin) reduces the hematopoietic response.

*Contraindications*: hypersensitivity to the drug, hypercoagulation, thromboembolism, erythrocytosis, erythremia.

*With extreme caution*, vitamin B12 should be used in patients at risk: with angina, with neoplasms, during pregnancy and lactation (teratogenic effects of high doses are not excluded).

When using vitamin B12, it is necessary to control the level of leukocytes and erythrocytes in peripheral blood and blood clotting.

*Prescription and dosage*. In the treatment of various manifestations and different stages of vitamin B12 deficiency – from 100–200 mcg per day subcutaneously up to 1000 mcg per day intramuscularly or intravenously, followed by the transition to prophylactic administration of 1000 mcg once a month (for anemia 100-200 mcg, with symptoms of funicular myelosis - 500 or more mcg daily for a week, and then every 5-7 days). In diseases of the central nervous system and peripheral nervous system - intramuscularly at 200-500 mcg per day for up to 2 weeks; with diabetic neuropathy 60-100 micrograms per day for 20-30 days.

Available in tablets of 100 mcg; in the form of a solution for injection in ampoules and 1 ml vials containing 30, 100, 200 and 500 mcg.

**Vitamin Bc - folic acid.**

*Mechanism of action and pharmacodynamic effects*. The active form of folic acid, tetrahydrofolic acid, is necessary for the synthesis of purine and pyrimidine bases, nucleic acids, and proteins. Provides erythropoiesis, leukopoiesis and cell division in various tissues, improves their trophism, regeneration of damaged tissues.

**Pharmacokinetics.**

*Absorption.* Folic acid, found in food and produced by intestinal bacteria, contains several residues of glutamate. It is absorbed only after their cleavage (only one remains) under the influence of intestinal conjugate. The activity of this enzyme is reduced in patients with sprue, chronic alcohol intoxication. Synthetic folic acidhas only one glutamic acid residue, which provides it rapid absorption from the gastrointestinal tract. Vitamin enters the blood within 30 minutes after taking it, the maximum concentration is reached after 30-60 minutes.

*Distribution and association with proteins*. Blood plasma contains folate-binding proteins, which are involved in the transfer of folic acid in the form of monoglutamate into cells. 90-95% of the absorbed vitamin enters the tissues within 3 minutes. Most of it is found in the liver and cerebrospinal fluid.

*Metabolism and elimination*. In the body, folic acid under the influence of reductases (with participation of vitamins B12 and C, biotin) is converted into tetrahydrofolic acid. A small part undergoes hepatic transformation. Most of it is excreted in the urine unchanged.

*Side effects.* Diarrhea and other dyspeptic symptoms when taking pharmacological doses. Increased excitability of the nervous system, insomnia, convulsions when using very large doses.

Hypertrophy and hyperplasia of the epithelium of the renal tubules and violation of their function with prolonged use of high doses.

Drug interactions. Triamterene, trimethoprim, sulfonamides, nitrofuran drugs, antibiotics, some antimalarials, methotrexate and cyclophosphamide reduce the effects of folic acid by interfering with its conversion to tetrahydrophilic acid. Cholestyramine, antacids interfere with absorption.

With simultaneous administration with phenytoin (difenin) and other antiepileptic drugs (phenobarbital, etc.), the amount of folic acid in the body decreases, which sometimes leads to the development of megaloblastic anemia.

*Contraindications*: hypersensitivity to the drug.

Folic acid should be used *with extreme caution* in patients of the group risk:
with neoplasms, in older age groups, in whose patients large doses of folic acid can cause vitamin B12 deficiency with corresponding neurological symptoms, in B12-deficiency anemia, when the appointment of folic acid without vitamin B12 may mask

the manifestations of anemia, but does not affect the symptoms of damage to the nervous system.

*Prescription and dosage.*

The prophylactic dose is 20–50 mcg per day. With a therapeutic purpose, it is prescribed orally at 0.5-1 mg 1-2 per day (up to 5 mg per day) for 20-30 days. During pregnancy, the daily dose is 400 mcg, and during lactation - 300 mcg.

Available in tablets of 0.001 g.

**Vitamin B15 is pangamic acid**.

Donator of methyl groups necessary for the synthesis of choline, methionine, creatine, catecholamines, steroid hormones, etc. Activates the respiratory enzymes of tissues, contributing to the preservation of their functions during hypoxia.

Pangamic acid deficiency has not been described in humans. For therapeutic purposes, it is used for hypoxia. The effectiveness of the application has not been proven. In clinical practice, calcium pangamate is used as a regulator of calcium-phosphorus metabolism. Assigned inside. Doses for adults are 50-100 mg 3-4 times a day. For children under 3 years old - 50 mg per day, 3-7 years old - 100 mg, 7-14 years old - 150 mg. The duration of admission is 20-40 days. Available in coated tablets of 0.05 g.

**Combined vitamin preparations (multivitamins)**

Multivitamin preparations are prescribed for the prevention of hypovitaminosis. Depending on the specific conditions, the relevant contingent, and, accordingly, on the indications, complexes containing different vitamins and their doses are selected (vitamins for pregnant women, the elderly, women of various age periods, children, for patients with diabetes mellitus, for taking during convalescence after various diseases and injuries, etc.). Most vitamins are not deposited in the body, and their excess is quickly excreted. However, in the absence of their deficiency, prolonged use in doses exceeding the daily requirement can lead to the development of hypervitaminosis, toxic reactions(see above). Therefore, the appointment of these drugs, like any other means, should be carried out in accordance with the indications.

Multivitamin preparations are not applicable for the treatment of hypo- and avitaminosis, other pathological conditions. Monocomponent preparations are used for treatment.

Indications for the use of individual vitamins are given in Table. 28.4.

**Table 28.4. The use of vitamins in clinical practice**

| Vitamin | General Medicine | Dentistry |
|---|---|---|
| A (retinol) | Hypo- and beriberi, rickets (together with vitamin D), hemeralopia, skin diseases, decreased infection resistance, hepatitis | Acceleration of epithelialization of erosions and ulcers, reduction xerostomia, normalization of metabolic processes in epithelium ORM (leukoplakia, lichen planus, cheilitis, cracked lips, etc.); in diseases periodontium as the basis for a medical dressing is used vegetable oils containing carotene (for example, rosehip oil) |
| D | Rickets, Fanconi syndrome, osteoporosis, osteomalacia,bone fractures, skin tuberculosis, hypoparathyroidism | Prevention and treatment of caries in children, periodontal disease,osteoporosis of the alveolar processes |
| E (tocopherol) | Diseases of the skin, cardiovascular system, peripheral vessels, infertility, threatening miscarriage, pathological menopause, dysmenorrhea, anemia, endocrine diseases, neurasthenia, chronic hepatitis, rheumatic diseases | Parodontosis, erosive and ulcerative lesions of the oral mucosa |
| C (ascorbic acid) | Treatment and prevention of hypo- and avitaminosis, disease Meller-Barrow, pregnancy, lactation, infections, diseases of the gastrointestinal tract; hypoxia, metabolic and respiratory acidosis, | Lesions of the oral mucosa with a hemorrhagic component, aphthous stomatitis, dyskeratosis, periodontal disease, Sjögren's syndrome, villous tongue, Kenon's nevus, candidiasis, viral and bacterial infections oral cavity, postoperative period |

| | | |
|---|---|---|
| | hemorrhagic diathesis, intoxication, radiation sickness, liver disease, sluggish wounds, ulcers, fractures, diseases skin, poisoning; in combination with vitamin D, iron preparations | |
| $B_1$ (thiamine) | Congenital disorders of thiamine metabolism, hypo- and avitaminosis, neuropathy, herpes zoster | Neuritis and trigeminal neuralgia, paresthesia oral mucosa, periodontitis, stomatitis, gingivitis, glossitis, cheilitis, secondary lesions of the oral mucosa with diseases of the gastrointestinal tract, diabetes, alcoholism, thyrotoxicosis |
| $B_2$ (riboflavin) | Hypo- and avitaminosis, hemeralopia, inflammatory eye diseases, asthenia, skin diseases, lack of proteins and excess carbohydrates in the diet, malnutrition, acute hypoxia, anemia, dysbacteriosis | Cheilitis, angular stomatitis, glossitis, Cannon's nevus |
| $B_3$ (PP, nicotine acid,nicotinamide) | Hypo-, avitaminosis, hereditary disorder tryptophan metabolism, atherogenic dyslipidemia, obliterating atherosclerosis, endarteritis, disease Raynaud | Lichen planus ORM, lupus erythematosus, periodontal disease, aphthous stomatitis, cheilitis, paresthesia, chronic lip fissure, atrophic bullous dermatitis, neuritis of the facial nerve |
| $B_5$ (pantothenic acid) | Diseases of the peripheral nervous system, neuromuscular disorders, eczema, | Desquamative glossitis, cheilitis |

| | | |
|---|---|---|
| | trophic ulcers, atony of smooth muscle organs. | |
| $B_6$ (pyridoxine) | Hypo-, avitaminosis, heart failure, hepatitis, sideroahrestic anemia, skin diseases, neuropathies, pellagra | Aphthous stomatitis, Sjögren's syndrome, glossalgia, cheilitis, neuralgia and trigeminal neuritis, nevus, periodontal disease |
| AT $_{12}$ (cyanocobalamin) | Hypo-, beriberi, including B12 deficiency anemia, malnutrition, degenerative changes in the central nervous system, traumatic, inflammatory and degenerative peripheral nerve damage, lateral amyotrophic sclerosis, encephalomyelitis, disseminated sclerosis, cerebral palsy, hepatitis, liver cirrhosis, skin diseases, radiation sickness | Trigeminal neuralgia, tongue paresthesia, ORM, lupus erythematosus, exudative multiforme erythema, periodontal disease, mucosal lesions in diabetes, alcoholism, drug-induced stomatitis |
| Vitamin $B_C$ (folic acid) | Hypo-, avitaminosis, including folic acid deficiency anemia, malnutrition, growth disorders of the child, enteritis, sluggish woundstest questions | Defects of the oral mucosa, lips in newborns |

Control questions

1. Indicate the wrong statement:

a) Vitamins A, D, E are fat-soluble.
b) The absorption of ascorbic acid increases in proportion to the increase in dose in all ranges.
c) Ascorbic acid has an antioxidant effect.
d) In chronic alcoholism, folic acid deficiency develops.
e) Hemorrhages on the oral mucosa are characteristic of vitamin C deficiency.

2. What is true about vitamin D?

a) Water soluble vitamin.
b) Used as an antioxidant.
c) Regulates phosphorus-calcium metabolism.
d) Absorbed in the oral cavity.
e) Quickly and completely excreted from the body.

3. What is wrong about vitamin A?

a) Has a cumulative effect.
b) Bile and fat are needed for absorption.
c) A non-protein bound vitamin is toxic.
d) Has a teratogenic effect.
e) Not metabolized in the body.

4. Indicate the wrong statement:

a) Activated charcoal reduces the absorption of vitamin A.
b) B vitamins are water-soluble.
c) Vitamin A is essential for normal growth and differentiation of the epithelium.
d) The active form of vitamin D is formed in bone tissue.
e) Large doses of folic acid may contribute to the development of vitamin B12 deficiency.

5. For vitamin B2 it is true:

a) With a deficiency, glossitis, angular stamatitis develops.
b) It is used for pernicious anemia.
c) Has a pronounced cumulative effect.
d) Bile is necessary for its absorption.
e) It is synthesized by the intestinal microflora in sufficient quantities.

6. When neuritis of the trigeminal nerve is used:

a) Vitamin A.
b) Vitamin E.
c) Vitamins B1, B6, B12.
d) Vitamin PP.
e) All of these vitamins.

7. What are the pharmacological effects of vitamin B1?

a) Participation in the Krebs cycle.
b) Participation in the conduction of a nerve impulse.
c) Participation in the regulation of "painful" activity of the nerve.
d) All of the above.
e) None of the above.

8. Vitamin deficiency contributes to:

a) Bowel disease.
b) Artificial feeding.
c) Hypoproteinemia.
d) Female gender.
e) All of the above.

9. What can cause vitamin D deficiency?

a) Chronic glomerulonephritis.
b) Insufficient exposure to the sun.
c) Taking anticonvulsants.

d) Impaired liver function.
e) All of the above.

10. What is not characteristic of vitamin B12 deficiency?

a) Macrocytic anemia.
b) Osteoporosis.
c) Hemolysis.
d) "Polished" language.
e) Pain in the tongue when eating.

# Chapter 29 Means affecting bone tissue. calcium supplements and fluorine.

Calcium and fluorine preparations belong to the group of agents that affect tissue metabolism and are involved in the formation of bones and hard tissues of the tooth.

*Classification*. Both calcium preparations and fluorine preparations can be both inorganic (calcium chloride, calcium carbonate, sodium fluoride, tin fluoride, monofluorophosphate) and organic (calcium gluconate, calcium glycerophosphate, calcium lactate, aminofluorides) compounds. All compounds of calcium and fluorine differ in the percentage of these elements in them.

## 29.1 CALCIUM PREPARATIONS

**Indications for use in dentistry:**

- ~ prevention and treatment of caries, osteoporosis of the alveolar bone, in particular with rickets and with an increased need for calcium (pregnancy, lactation, period of intensive growth in children);
- ~ prevention and treatment of non-carious lesions of hard tissues of the tooth, including fluorosis.

*Mechanism of action and main therapeutic effects.*

In the body of an adult, the calcium content is 20 g per 1 kg of body weight. Its main part (99%) is concentrated in bone and cartilage tissues and teeth, where in combination with phosphorus, it forms a mineral base. Calcium inhibits osteoclast activity and inhibits bone resorption.

In the teeth, calcium and phosphorus are present in the form of calcium hydroxyapatite [Ca10(PO4)6(OH)2] and calcium apatite fluorophosphate Ca5F(PO4)3. The concentration of calcium in tooth enamel is 1.4 times higher than in dentin. Violation of phosphorus-calcium metabolism leads to enamel demineralization and a decrease in the resistance of tooth tissues to adverse external influences. In intact teeth in young people, on average, the ratio of calcium and phosphorus is 2.07; in persons over 30 years old - 1.97.

This ratio reaches the maximum value in the enamel of the canines (2.29), the minimum - in the enamel of the incisors (1.66). The content of calcium and phosphorus increases in the direction from enamel-dentin border to the enamel surface. In caries, the ratio of calcium to phosphorus is lower than in healthy enamel.

The calcium content in the oral fluid plays an important role in the regulation of metabolism fluorine (see below).

Enamel and dentin are permeable in both directions: from the enamel surface to the dentin and pulp, and from the pulp and dentin to the enamel surface. Various minerals, amino acids, vitamins, enzymes, carbohydrates, etc. penetrate through the enamel.

Enamel permeability is an important condition for the effectiveness of topical preparations. Enamel permeability is influenced by various factors.

(Table 29.1).

**Table 29.1. Factors affecting pronienamel wear**

| Raise | Downgrade |
|---|---|
| Acids | Alkalis |
| Deficiency of phosphorus salts in food | Calcium hydroxide |
| Calcitonin | Parathormone |
| Urea | A complex of age-related factors |

In addition to its structural function, calcium has many biochemical and physiological effects. Biologically active is ionized calcium, which is about 0.1% of its total amount in the body. Calcium ions are involved in the regulation of the formation and accumulation of energy, the permeability of biological membranes, in the release of mediators, the activation of a number of enzymes, blood coagulation, processes of excitation and muscle contraction.

Normal plasma calcium concentration is 2.3–2.75 mmol/l.

**Pharmacokinetics.**

*Absorption*. Under physiological conditions, calcium is supplied with food and absorbed in the gastrointestinal tract. Its absorption from the lumen of the small intestine is carried out by two mechanisms - active transport and passive diffusion. In the form of inorganic salts, it is absorbed worse than from compounds with organic substances.

Tableted forms of glycerophosphate and calcium lactate are poorly soluble, therefore, the release of the active substance is not complete, which limits its bioavailability. These forms are ineffective.

*Communication with plasma proteins*. In plasma, about 45% of calcium is in complexes with proteins.

*Distribution in the body.* The main amount of calcium entering the bloodstream is deposited in bone tissue. With insufficient intake from food, its content in the blood is maintained by leaching from the bone depot.

*Elimination.* During the day, the kidneys filter up to 275 mmol of calcium, but only 0.5–1% of this amount is excreted in the urine.

The main factors that regulate phosphorus-calcium metabolism and maintain a stable concentration of calcium in the blood are vitamin D, parathyroid hormone (parathormone), thyroid-stimulating hormone, thyrocalcitonin.

In addition to them, glucocorticoid and sex hormones, ascorbic acid, B vitamins, prostaglandins, and microelements are involved in the regulation of calcium metabolism.

The absorption of calcium is facilitated by its combination with magnesium. Magnesium deficiency leads to a decrease in the level of calcium in the blood, even with sufficient intake of the latter with food. The content of calcium, magnesium and phosphorus in the oral fluid affects the mineralization of enamel and the severity of dental caries.

*Unwanted actions.*

Systemic side effects may appear:

- ~ hypercalcemia (at a dose of more than 2000 mg of calcium / day);
- ~ when ingesting large doses, especially against the background of a milk diet - hypercalcemia or milk-alkaline syndrome (headache, weakness, anorexia, nausea, vomiting, abdominal pain, constipation, thirst, kidney damage, polyuria);
- ~ with intravenous and intramuscular administration - dyspeptic symptoms (nausea, vomiting,diarrhea), bradycardia;
- ~ with a / in the introduction of a burning sensation in the mouth, a feeling of heat;
- ~ with fast introduction - a decrease in blood pressure, arrhythmia, syncope, cardiac arrest.

Local side effects primarily include dyspeptic symptoms (pain in the epigastrium, flatulence, diarrhea, constipation) and secondary hyperacid syndrome when taken orally, as well as necrosis in the area of intramuscular injection.

*Contraindications.*Hypercoagulation, severe atherosclerosis, hypercalcemia, i.e. plasma concentration of more than 3 mmol / l (hyperparathyroidism, vitamin D overdose, bone metastases), severe renal failure, hypercalciuria, calcium urolithiasis, multiple myeloma, sarcoidosis, phenylketonuria, intoxication with cardiac glycosides.

*With extreme caution,* correcting doses, and only according to strict indications, it should be used in patients with diarrhea, poor absorption syndrome, chronic circulatory failure, as well as in childhood with intramuscular injection (risk of necrosis).

Use during pregnancy and lactation is not contraindicated.

**Drugs**

*Calcium gluconate* (calcium gluconate, calcium gluconate tablets 0.5 g, calcium gluconate injection 10%) has a less pronounced resorptive effect than other calcium salts.

*Prescription and dosage*. Inside - two to three times a day before or 1-1.5 hours after a meal, drinking milk. Single dose: 1–3 g for adults, 0.5 g for children under one year old, 1.0 g for children from 1 to 4 years old, 1–1.5 g for children from 5 to 6 years old, 1, 5-2.0 g - for children from 7 to 9 years old. In / in or / m for adults, 5-10 ml of a 10% solution daily or every other day, for children, depending on age, from 1 to 5 ml of a 10% solution every 2-3 days.

Application or by electrophoresis (remineralizing therapy) - 10% solution for 10–15 minutes (with remineralizing application therapy according to E.V. Borovsky - 5–20 min) on the surface of the teeth.

Release form: tablets of 0.5 g, 10% solution for injection in ampoules of 10 ml.

*Calcium carbonate* (calcium additive, vitacalcin, calprimum, precipitated calcium carbonate) - in addition to influencing phosphorus-calcium and electrolyte metabolism, it neutralizes hydrochloric acid and reduces the acidity of gastric juice.

*Prescription and dosage.* 0.25-1 g 2-3 times a day with 200 ml of water (dissolve an effervescent tablet in a glass of water) or at night.

Release form: effervescent tablets of 4.2 g (500 mg of calcium), tablets of 0.25 g, coated tablets for chewing 0.5 g, substance-powder in packages of 5 and 10 mg.

## 29.2 FLUORINE PREPARATIONS

The ability of fluorides to prevent cavities and tooth decay was discovered during experiments by Dr. Basil Bibby in the early 1940s. The doctor found that if a little fluoride was applied to a cotton swab and applied to an aching tooth, the zuyu could be saved.

*Indications for use in dentistry*: prevention and treatment of caries.

*Mechanism of action and main therapeutic effects*. In nature, in the human body and in preparations used for the prevention of dental caries, it is not chemically pure fluorine that is contained, but its compounds - fluorides.

Fluoride attacks tooth enamel and plaque bacteria. It is involved in the formation of organic compounds of phosphorus, the binding of calcium and phosphate by tissues, stimulates the development of teeth and jaws in children. With a constant supply of fluoride, calcium fluoride microcrystals form on the enamel surface. When they interact with calcium phosphate and proteins contained in saliva, hydroxyapatite in the surface

layers of enamel turns into acid-resistant fluorapatite. Regular intake of even small amounts of fluoride and maintaining a stable concentration in the environment surrounding the tooth is sufficient to maintain the resistance of the enamel.

Fluorine compounds found in saliva and plaque disrupt the transport of glucose into bacterial cells and the formation of extracellular polysaccharides, forming the dental plaque matrix. Fluoride inhibits the formation of organic acids by increasing the pH of saliva. When the pH of the oral fluid decreases, calcium fluoride becomes unstable, releasing fluorine ions, which react with calcium ions and phosphates released from the enamel during the formation of a carious lesion.

This leads to the re-formation of fluorapatite, preventing the progression of caries.

The use of fluoride is most effective in the presence of initial carious lesions, its effect on healthy enamel is less pronounced. It does not so much prevent the formation of caries as it inhibits its spread.

Fluoride affects the enamel throughout life and therefore its use is rational in all age groups. If fluoride is supplied after teething, it reduces the solubility of enamel, promotes remineralization of partially demineralized enamel.

Fluoride is able to prevent the development of caries of the tooth root.

**Pharmacokinetics.**

*Absorption.* Fluoride naturally enters the body with food and drinking water and is absorbed in the gastrointestinal tract. The absorption of medicinal fluoride does not depend on food intake and is 93-97%. The maximum plasma concentration is reached after 4 hours.

*Distribution in the body*. Most of the fluoride absorbed in the gastrointestinal tract is deposited in the bones and teeth, from where it can be re-introduced into the blood as needed. The accumulation of fluoride in the teeth occurs mainly in areas that are in contact with circulating fluids (in the surface of the enamel or in the dentin, adjacent to the pulp). The maximum amount of fluoride is determined in the surface layer of the enamel of the molars, the minimum - in the area of the enamel-dentine border of the incisors.

Fluoride intensively accumulates in the tissues of the tooth during the formation of the crown and in the first years after eruption, when the mineralization of the tooth occurs. The concentration of fluoride in temporary teeth is lower than in permanent teeth. With age, its content in permanent teeth decreases, which is explained by the gradual loss of enamel as a result of abrasion.

*Elimination*. Fluoride is excreted from the body mainly in the urine. Under the age of 15, 50% of the fluoride that enters the body per day is excreted in the urine, at 16–19 years - 55%, aged 20 years and older - 60%.

The salivary glands secrete very little fluoride and its content in saliva as well as in dental plaque is low. With local or systemic use of fluorine preparations, its content in saliva increases. So, immediately after rinsing with a 0.05% sodium fluoride solution, the level of fluoride in saliva increases to an average of 3 mmol/l and remains elevated for an hour.

With a sufficient content of calcium in the oral fluid, calcium fluoride is formed, which is more slowly eliminated than sodium fluoride. Therefore, the calcium content in the oral fluid affects not only the state of enamel hydroxyapatite, but also the fluorine kinetics.

*Side effects and toxicity.* Allergic reactions - mainly in the oral cavity, when using topical forms. Dyspeptic symptoms (nausea, vomiting). Pain in the legs and joints Increased fatigue, general weakness, headache.

**Fluorosis** ("spotted enamel"). The risk of developing fluorosis is highest in children under 2–2.5 years. It is believed that with a daily intake of fluorine in a dose not exceeding 0.1 mg/kg body weight risk of developingfluorosis is minimal. At the same time, according to WHO experts, when using fluoride-containing products, it is impossible to achieve a preventive effect and avoid the appearance of weak forms of fluorosis. Thus, with the optimal fluorine content in water of 1 mg/l, fluorosis develops in 15–20%, but it is mild and is not a cosmetic or clinical problem.

Osteosclerosis, ectopic calcification (especially when combined with vitamins D or A). Hypothyroidism - when taking fluoride orally. Acute intoxication - lacrimation, hypersalivation, anorexia, nausea, vomiting, bloody diarrhea, pain in the abdomen, legs and joints; constriction of the pupils, blurred vision; weakness, myasthenia gravis, tremor, convulsions, hyperthermia, tachycardia, hypotension, respiratory failure, respiratory arrest. Treatment is fluid infusion, solutions of calcium gluconate, lactate, oral milk and calcium preparations, induction of vomiting, gastric lavage with 1% calcium chloride solution, saline laxatives, symptomatic therapy.

When analyzing the balance of fluoride in the body, it is necessary to take into account all sources of fluoride intake, including drinking water and food products.

*Contraindications.* The content of fluorides in drinking water, exceeding the optimum - 1 mg / l or 0.05mmol / l (in hot climates - 0.7 mg / l or 0.037 mmol / l). Allergic reactions. Pronounced violations of the liver and kidneys. Hypothyroidism. Peptic ulcer of the stomach and duodenum in the acute stage. Children's age (up to 6 months, 3 years, 6 years or 16 years - depending on the dosage form and dose).

The use of fluoride-containing drugs during pregnancy and lactation is contraindicated.

*Risk groups for side effects*: patients with blood diseases, children under 6 years of age (take into account the total fluoride content in drinking water and food).

*Drug and food interactions.*Antacids, calcium, magnesium, aluminum ions (both in preparations and in food products) disrupt absorption, forming poorly soluble complexes. Vitamins D and A contribute to ectopic calcification.

*Clinical Application.* In clinical practice, fluorides are used both systemically and locally. Systemic application - the introduction of fluoride into the body with fluoridated water, salt, milk, and also in tablets or drops. Systemic methods are indicated for a high incidence of caries among the population and a low fluoride content in drinking water (less than half the dose optimal for a given climate). System methods should not be used in combination.

*Water fluoridation*. The optimal concentration of fluoride is 1 mg/l or 0.05 mmol / l (in hot climates - 0.7 mg / l or 0.037 mmol / l). The best results are achieved by drinking fluoridated water from an early age. At the same time, infants receiving fluoridated water formulas are at risk of developing fluorosis. If fluoridated water is used after teething, it only affects teeth that are less than 2-3 years old.

The clinical efficiency of the method is 50–70%.

*Milk fluoridation*. Calcium and phosphate contained in milk improve the process of remineralization of teeth, although they reduce the systemic bioavailability of fluoride.

The amount of the latter added to milk is calculated taking into account its content in water and other products (daily intake of fluoride by children aged 3 to 7 years should not exceed 0.87-1.75 mg). According to the recommendations of WHO experts, children aged from 3 to 12 years of age should receive 200 ml of fluoridated milk daily for at least 250 days a year.

The clinical efficiency of the method is 50–60%.

*Fluoridation of table salt.* For 1 kg of salt add 250 mg (13.2 mmol) fluoride. This method is not very reliable due to large fluctuations in salt intake, depending on the traditions of the country and individual eating habits.

*Clinical efficiency* - about 40%.Sodium fluoride (sodium fluoride, sodium fluoride for children, ossin) - is used to prevent dental caries when the fluoride content in drinking water is less than 0.5mg/l.

*Multivitamin + multimineral (Vitafor)* - combined preparation, consisting of sodium fluoride, retinol, ergocalciferol and ascorbic acid.

Treatment is most effective if started no later than 2 years after the birth of the child.

*Prescription and dosage.*

Vitafor in oral solution for children from 1 to 6 years old is prescribed ½ teaspoon per day; children from 7 to 14 years old - 1 teaspoon per day. Course duration 1 month, 4-6 courses per year; the interval between courses is at least 2 weeks.

Doses of Vitafor tablets are presented in Table 29.2.

**Table 29.2. Dosing of Vitafor when the fluoride content in drinking water is less than 0.5 m / l (according to E.M. Kuzmina and T.A. Smirnova, 2001)**

| Age (years) | Daily pills | Fluoride content (mg) |
|---|---|---|
| 2-4 | 0.5 | 0.25 |
| 5– 6 | 1 | 0.5 |
| 7-14 | 2 | 1.0 |

Release form - solution for internal use (vials), 115 ml.

Topical administration - use of toothpastes, varnishes, rinses, application gels, sealants (silants), filling materials.

*Fluoride-containing agents* for topical use contain more fluoride and have a local effect in the oral cavity - they promote remineralization in case of early carious damage, demineralization of tooth enamel. All local prophylactic agents have approximately equal efficacy and their choice for a given patient depends on cost, ease of use and safety.

*Toothpaste*. The composition may include various fluorides - sodium fluoride, tin, monofluorophosphate, sodium fluoride acidified with phosphates, or organic fluorine compounds - aminofluorides. All these compounds have approximately equal efficiency. Brush your teeth with toothpaste for 3 minutes 2 times a day. Clinical efficiency with regular use is 30 - 40%. Since there is a risk of children swallowing toothpaste when brushing their teeth, fluoride-containing toothpastes can be used in children from 2 to 3 years of age, and only under parental supervision.

*Fluoride-containing varnishes* - allow you to extend the period of exposure to fluoride, forming a film adjacent to the enamel, which remains on the teeth for several hours.

They are used at a moderate or high level of intensity of dental caries in a population of children and adolescents with a high risk of developing caries. The frequency of application of varnish 2 - 4 times a year. Clinical efficiency -20 - 70%.

*Fluoride-containing solutions and gels for professional use* -(sodium fluoride - 2% solution; sodium fluoride acidified with phosphoric acid in the form of a solution and a gel containing 1.23% fluoride. Phosphate prevents enamel demineralization). Apply in the form of rinses or applications 1 - 2 times a year, after cleaning the teeth from plaque. Clinical efficiency 30 - 50%. For gel applications the patient swallows part of the dose (average 30%), so the gels are used with caution, especially in children. When performing the application, a saliva ejector should be used, and after the end of the procedure, rinse your mouth for a minute.

*Fluoride-containing solutions for self-use* - 0.05% solution.

*Sodium fluoride* - rinsing frequency 1 time per day; 0.1% - once a week; 0.2% - 1 time in two weeks. The duration of the rinse is 1 minute.

Apply after the eruption of the first permanent teeth. After the end of the application, the effect persists for 2-3 years.

*Clinical efficiency* - 30 -40%. For children under 6 years of age, rinsing is not recommended, and for younger students, the volume of rinsing should not exceed 5 ml (risk of swallowing).

*Sealants* and filling materials that gradually release fluoride.

Sealants, which include fluoride, are applied to the enamel of the chewing surface of the teeth that is not affected by caries in order to protect it from the microflora of the oral cavity and its metabolic products, acids and other factors that demineralize the enamel. Sealants last much longer than varnishes. Indication for their use - high risk of dental caries.

For filling, special glass ionomer cements are used, containing up to 20% fluorides, capable of not only releasing, but also accumulating fluorine ions upon contact with fluoride-containing topical agents. During the first three months after the filling, the release rate of fluorine ions is quite high, but then it decreases and remains stable for many years. The antimicrobial action of fluoride prevents the adhesion of bacteria to the surface of the filling and the contact surfaces of the adjacent tooth.

Since the release of fluoride is slow, the risk of developing intoxication when using sealants and special filling cements minimum.

## Control questions.

1. Enamel permeability increases:

a) vitamin D
b) parathormone
c) phosphorus deficiency
d) vitamin A
e) all of the above factors

2. In the regulation of phosphorno-calcium metabolism does not take part:

a) vitamin D
b) thyroid-stimulating hormone
c) parathyroid hormone
d) vitamin PP
e) fluoride

3. Calcium absorption is increased by all substances except:

a) aluminum
b) magnesium
c) vitamin C
d) selenium
e) fluorine

4. Taking calcium supplements is contraindicated in:

a) rickets
b) hypercalcemia
c) arterial hypertension
d) osteomalacia
e) bronchial asthma

5. Side / undesirable effects of calcium preparations:

a) hypercalcemia
b) soft tissue necrosis with intramuscular injection
c) bradycardia
d) nephropathy
e) all of the above

6. Side effects / undesirable effects of fluorine preparations for systemic use:

a) dyspeptic symptoms
b) hypothyroidism
c) fluorosis
d) all of the above
e) only C

7. Specify the minimum acute toxic dose of fluoride for children:

a) 2.5mg/kg
b) 5 mg/kg
c) more than 5 mg/kg
d) 7.5 mg/kg
e) all of the above doses are toxic

8. Incorrect statement:

a) Systemic methods of fluoride application are indicated for high incidence of dental caries in the population and low fluoride content in drinking water.
b) The use of fluoride is most effective in preventing caries
c) Sufficient calcium in the oral fluid increases efficiency treatment with fluorides
d) Fluoride has a bacteriostatic effect on the microflora of the oral cavity
e) Excess fluoride is excreted from the body with urine

9. Indicate the correct statement:

a) Children under 2-2.5 years of age are at risk of developing fluorosis
b) The use of fluoride is most effective in older age groups
c) The most effective prevention of dental caries is with a combination of systemic methods of fluoride administration.
d) Pregnancy is an indication for prescribing sodium fluoride tablets
e) All of the above are correct

10. Valid for local forms of fluoride:

a) promote remineralization in case of early carious damage
b) have approximately equal efficiency
c) when used in young children, toxic effects may develop
d) when used, local allergic reactions are possible
e) all of the above is true.