

INTRODUCTION

General Pharmacology

Pharmacology is the science dealing with biochemical and physiologic aspects of drug effects, including absorption, distribution, metabolism, elimination, toxicity doses, and specific mechanisms of drug action. Pharmacology includes three major divisions: theoretical (general), experimental, and clinical. Theoretical pharmacology touches upon common regularities of interactions of drugs with an organism. Experimental pharmacology investigates drugs influence on the organism of animals. Clinical pharmacology examines drugs influence on the organism of patient. Pharmacotherapy studies the use of medicaments for cure of a concrete illness. Some branches of pharmacology are different sciences: phytotherapy, toxicology, vitaminology, endocrinology, and chemotherapy. Pharmacology is closely connected with pharmacy. Pharmacology is based on the advances of physics, chemistry, biology, biochemistry, physiology for the explanation of drugs mechanism of action. Pharmacology is the basis for therapy and other clinical disciplines. The **pharmacological effect** is the changes of metabolism and function of cells. **Mechanism of action** is the way by means of which the initial reaction is realized. The **initial pharmacological reaction** is characterized by biochemical, physiological, physical and chemical changes of metabolism and function of systems and organs. The two main areas of pharmacology include pharmacokinetics and pharmacodynamics. **Pharmacokinetics** refers to the way the body handles drug absorption, distribution, biotransformation, and excretion. **Pharmacodynamics** is the study of biochemical and physiological effects of drugs and their mechanisms of action.

PHARMACOKINETICS

Drug transport. The movement of drug molecules in the body is subject to absorption, distribution, and excretion. Drugs can cross cellular membranes by various mechanisms. The mechanisms of absorption are similar to the mechanisms of membrane transport: passive diffusion, carrier-mediated diffusion, filtration, active transport, or pinocytosis. Being a bimolecular lipid layer, the cell membrane can also

act as a barrier to some drugs.

Passive diffusion. Most compounds penetrate into cells by diffusing as the **un-ionized moiety** through the lipid membrane. Factors affecting the passage of a molecule through a membrane are the molecule's size and charge, the lipid-water partition coefficient, and the concentration gradient. The two types of passive drug transport are **simple diffusion** and **filtration**.

Simple diffusion. Simple diffusion is characteristic of organic acids and alkaline. The greater the concentration gradient, the greater the rate of absorption. The larger the absorbing surface, the greater the drug flux. The diffusion constant is directly proportional to the temperature and is inversely related to the molecular size. The greater the lipid-water partition coefficient, the greater the drug flux. In simple diffusion, molecules cross the lipid membrane in an **uncharged form**. The pH of the medium affects the absorption and excretion of a passively diffused drug. Acidum acetylsalicylicum and other weak acids are best absorbed in the stomach because of its acidic environment. Alkaline drugs are best absorbed in the small intestine, which has a higher pH.

Filtration is a character of urea pure. Water, ions, and some polar and non-polar molecules of low molecular weight can diffuse through membranes, suggesting that **pores** or **channels** may exist. The capillaries of some vascular beds (e.g. in the kidney) have large pores, which permit the passage of molecules as large as proteins.

Carrier-mediated facilitated diffusion is character of amino acids, vitamins and other drugs. In this type of transport, movement across the membrane is facilitated by a macromolecule. It is a saturable process; that is, external concentrations can be achieved in which increasing the external/internal concentration gradient will not increase the rate of influx. It is selective for the chemical structure of a drug; that is, the carrier mechanism transports only those drugs having a specific molecular configuration. It requires no energy. It cannot move against a concentration gradient and, therefore, is still diffusion.

Active transport is a character of cardiac glycosides and others. Active transport is similar to carrier-mediated diffusion in several ways: movement across

the membrane is mediated by macromolecules. It is a saturable process, selective for chemical structure. Several important features distinguish active transport from diffusion processes. Active transport requires metabolic energy; this is often generated by the enzyme known as $\text{Na}^+\text{-K}^+\text{-ATPase}$. It transports molecules against a concentration gradient.

Pinocytosis is typical of lipid soluble vitamin drugs. A vacuolar apparatus in some cells is responsible for this process. There exist both **fluid-phase pinocytosis** for substances such as sucrose and **adsorptive-phase pinocytosis** for substances such as insulin.

Bioavailability is the relative rate and extent by means of which a drug reaches the general circulation; this is especially important when a drug is administered orally. Factors that influence bioavailability are: solubility of the drug in the contents of the stomach, dietary patterns, tablet size, quality control in manufacturing and formulation.

Absorption is the rate at which a drug leaves the site of administration and the extent to which this occurs. The absorption of a drug through the mucosal lining of the gastrointestinal tract or through capillary walls depends on the physical and chemical properties of the drug.

Route of administration is an important determinant of the rate and efficiency of absorption.

Enteral routes are the most common routes of administration. **Examples of enteral routes are** peroral, rectal, sublingual, subbuccal, and duodenal. **Advantages of peroral administration.** An alimentary route is physiological, generally the safest route of administration. The delivery of the drug into the circulation is slow after oral administration, so that rapid, high blood levels are avoided and adverse effects are less likely. The dosage forms available for alimentary administration are convenient and do not require sterile technique.

Disadvantages of alimentary administration. It is not convenient for the first aid. The main disadvantage is that the rate of absorption varies. It becomes a problem if a small range in blood levels separates a drug desired therapeutic effect from its

toxic ones. Irritation of mucosal surfaces can occur. A patient compliance is not ensured. With peroral administration of some drugs extensive hepatic metabolism may occur before a drug reaches its site of action. This is known as a first-pass effect. Passage through the liver and the resulting initial hepatic metabolism are avoided by administering the drug sublingually. But only some drugs may penetrate through mucose surfaces.

Parenteral routes. The main merit is that the medicine bypasses the alimentary tract. **Examples of parenteral routes:** intravenous, intramuscular, subcutaneous, intraperitoneal, intra-arterial, intrathecal, transdermal, intranasal, and inhalational etc.

Advantages of parenteral administration. A drug gets to the site of action faster, providing a rapid response, which may be required in an emergency. The dose can often be more accurately delivered. Parenteral administration can be used when the alimentary route is not feasible (e.g. when a patient is unconscious). Large volumes can be delivered intravenously.

Disadvantages of parenteral administration. More rapid absorption can lead to increased adverse effects. A sterile formulation and an aseptic technique are required. Local irritation may occur at the site of injection. Parenteral administration is not suitable for insoluble substances. Parenteral administration may lead to HIV infection and phlebitis.

Topical administration is useful in the treatment of patients with local conditions; with topical administration there is usually little systemic absorption. Drugs can be applied to various mucouse membranes and skin. **Inhalation** provides a rapid access to circulation; it is the common route of administration for gaseous and volatile drugs. It is managed well. In the case of inhalation there may occur allergic reaction and any disease may be aggravated.

Factors affecting drug absorption. Solubility of a drug in water and lipid affects absorption. **Dosage** affects the drug concentration at its site of action and, thus, greatly influences a biologic response to a drug. The larger the dose, the greater the effect, until a maximum effect is achieved. This is called a **dose-response**

relationship. A **route of administration** affects the area of absorbing surface available to a drug. Drugs are absorbed more quickly from large surface areas. After any route of administration except intravenous administration the absorption of most drugs follows **first-order (exponential) kinetics**; thus, a constant *fraction* of drug is absorbed. After intravenous administration a constant *amount* (i.e. 100%) of a drug is absorbed. After absorption or injection drugs may be distributed into interstitial or cellular fluids. **Drug distribution** may be uniform and nonuniform. Once in the circulatory system, some drugs can **bind** nonspecifically and reversibly to various **plasma proteins**; that is, to albumin or globulins. In this case, a bound and free drug reaches equilibrium. Only a **free drug** exerts a biologic effect; a bound drug stays in the vascular space, and is not metabolized or eliminated. Some areas of a body (e.g. the brain) are not readily accessible to drugs due to **anatomic barriers** (haemato-encephalic etc.). The placenta also provides a barrier to some drugs. The drugs may be **sequestered** in storage depots; for example, lipid-soluble drugs in a fatty tissue. Factors modifying the **distribution** of a drug to a particular region of the body: physical and chemical characteristics of the drug (lipid to water partition coefficient); the velocity of blood circulation and cardiac output; capillary permeability in various tissues; lipid content of the tissue; binding to plasma proteins and tissues; disposition to tissues.

Clinical distribution. One-compartment model. This is the simplest and most commonly used pharmacokinetic model system. Usually distribution of a drug within a compartment is assumed to be **uniform**. The **apparent volume of distribution** (V_d) is a quantitative estimate of the tissue localization of a drug. It can be determined by measuring the plasma level of the drug:

$$V_d = \frac{\text{total amount of drug in body}}{\text{concentration of drug in plasma}}$$

In general, a high V_d indicates high lipophilicity or many receptors for a drug. The **total body clearance** is a volume of blood or plasma that is effectively cleared a drug in a specified unit of time. Clearance is related to V_d and to the time required for plasma drug concentration or the amount in the body to decrease by 50%, which is

called half-life ($t_{1/2}$). Clearance is, therefore, related to the elimination rate constant (k):

$$\begin{aligned} \text{Clearance} &= V_d (k) \\ &= \frac{V_d (0.693)}{t_{1/2}} \end{aligned}$$

This formula assumes a specific V_d , but the V_d changes over the time.

Two-compartment model is generally used for drugs which are not administered intravenously because it can better describe both distribution and elimination. **The multicompartment model** is used for drugs which are stored in body depots and for drugs with extensive metabolism or elimination mechanisms.

Drug metabolism /biotransformation is the process of a chemical alteration of drugs in a body. The main principles are: a liver is a major site of metabolism for many drugs or other xenobiotics, but other organs, such as lungs, kidneys and adrenal glands can also metabolize drugs. Many lipid-soluble, weak organic acids or bases are not readily eliminated from a body and must be conjugated or metabolized to compounds which are more polar and less lipid-soluble before being excreted. Metabolism results in **inactivation** of a compound (e.g. morphini hydrochloridum). Some drugs are **activated** by metabolism. Some of these substances are called **prodrugs** (e.g. enalaprilum). Some drugs become more toxic by biotransformation.

Biochemical reactions involved in drug metabolism occur in two phases:

Phase 1: reactions are divided into: a) microsomal oxidation; b) nonmicrosomal oxidation (e.g. oxidation, reduction, hydrolysis) after chemical reactivity and increase aqueous solubility;

Phase 2: reactions (e.g. conjugation) further increase solubility, promoting elimination.

Oxidation, the most common metabolic reaction, involves addition of oxygen or removal of hydrogen from a drug.

Microsomal oxidation. A smooth endoplasmic reticulum of cells in many organs, especially in a liver, contains **membrane-associated enzymes**, which are responsible for drug oxidation. Primary components of the enzyme system are

cytochrome P-450 reductase and **cytochrome P-450**. There are some types of microsomal oxidation reactions: carbon oxidation-hydroxylation of aliphatic or aromatic groups (e.g. aminazinum and dipheninum), *N*- or *O*-dealkylation (e.g. caffeinum), *N*-oxidation or *N*-hydroxylation (e.g. 2-acetylaminofluorenum), sulfoxide-oxidation (e.g. dimethylsulfoxidum), deamination (e.g. phenaminum), desulfuration (e.g. thiopentalum-natrium).

Nonmicrosomal oxidation. There are soluble enzymes found in the cytosol or mitochondria of cells, which are responsible for metabolism of relatively few compounds. Such enzymes, for example, include: **alcohol dehydrogenase** and **aldehyde dehydrogenase**, which oxidize ethanol to acetaldehyde and acetate. **Monoamine oxidase** is important to the metabolism of catecholamines and serotonin.

Reduction occurs both in microsomal and nonmicrosomal metabolizing systems. Examples of microsomal reduction include laevomycetinum. Examples of nonmicrosomal reduction include aldehyde (chlorali hydrats), ketone (naloxoni hydrochloridum).

Hydrolysis. Nonmicrosomal hydrolysis may be in a variety of body systems, including plasma. Examples of **nonmicrosomal hydrolysis** are nonspecific **esterases** for drugs, such as acetylcholine, succinylcholine, and Novocain etc.

Glucuronide conjugation is the most common conjugation reaction. It occurs frequently with phenols, alcohols, and carboxylic acids. Glucuronides are generally inactive and are rapidly excreted in urine or bile by anionic transport systems. Glucuronides eliminated in the bile can be hydrolyzed by intestinal or bacterial β -glucuronidases and free drug can be reabsorbed. Such **enterohepatic recirculation** can greatly extend the action of a drug.

Other conjugation reactions. Sulfate formation in which phenols, alcohols, and aromatic amines are converted to sulfates and sulfanilates; 3'-phosphoadenosine 5'-phosphosulfate (PAPS) is the sulfate donor (e.g. steroids); *O*-, *S*-, and *N*-methylation; *S*-adenosylmethionine is a methyl donor (e.g. noradrenalinum hydrochloridum); *N*-acetylation; acetyl coenzyme A is an acetyl donor (e.g.

isoniazidum); glycine and glutamine conjugation with acids (e.g. acidum salicylicum); glutathione conjugation (e.g. acidum ethacrynicum).

Factors affecting drug metabolism are the similar (equal) to the factors influencing the interaction of drugs with organism.

The factors from drugs are:

1. Sources of reception: plants (galenical – e.g. tincture Valerianae, new galenical drugs – e.g. corglyconum); glycosides (e.g. strophanthinum, digoxinum); animals (e.g. hormones, enzymes); minerals (e.g. magnesii sulfas); microorganisms (e.g. tetracyclinum); the products of chemical synthesis (e.g. captoprylum); gene-engineering technology (e.g. insulinum).

2. Physical and chemical properties of drugs: aggregate status, extent of volatility making small and dissociation solubility in water and lipids, isomery and stereoisomery, mass, charge. Certain drugs may stimulate or inhibit metabolism of other drugs (e.g. phenobarbital stimulates the metabolism of diphenylhydantoin).

Drugs form consists of main and relieving components which determines the type of drug action.

3. Way of administration. An oral route, for example, can result in extensive hepatic metabolism of some drugs (the first-pass effect). Starvation can deplete glycine stores and alter glycine conjugation.

4. Duration of the action and the period of administration of hormones, chemotherapeutic drugs must be defined.

5. Drug administration turn (e.g. tetracyclinum with calcii gluconas may be complex). The drug administration turn must be approved one after another.

6. A drug interaction may be:

a) physical and chemical, pharmaceutical interaction in drugs form, in blood, in a stomach – intestinal tract;

b) pharmacological interactions are synergism and antagonism.

7. Dosage and concentration. The dosage is the quantity of drugs in the units of mass, volume and biological activity. Concentration is an extent of a drug in solvent or biological liquids. There are therapeutical, prophylactic, toxic, and lethal doses.

Therapeutical doses may differ as a single, daily and course doses. Doses may be minimal, average, and maximal. They may be divided into a stroke, support, divided, and prophylactic doses.

The factors from organism are:

1. **Species of animals** (e.g. frogs, cats, and pigeons are more sensitive to cardiac glycosides).

2. **Age.** A liver cannot detoxify drugs as well in neonates as it can in adults. Elderly patients may absorb drugs less completely or slower, drugs distribution may be altered by hypoalbuminemia, metabolism may be unpaired by reduction of enzyme activity, hepatic mass, and blood flow. Excretion may be braking. Children have different process of absorption, distribution, biotransformation, and excretion than adults. Doses of toxic and powerfully acting drugs may be found in the guide-books. Children doses of other drugs may be calculated according to the following formulae:

$$\text{Children dose} = \frac{\text{Adults dose} \times \text{child age}}{24};$$

$$\text{Children dose} = \frac{\text{Adults dose} \times \text{child age}}{\text{child age} + 12};$$

$$\text{Children dose} = \frac{\text{Adults dose} \times \text{child mass}}{70 (\text{average adults mass})} \times \text{doses factor};$$

$$\text{Children dose} = \frac{\text{Adult dose} \times \text{child body surface (coefficient } t)}{1,73\text{m}^2 (\text{average adults' body surface})};$$

The drugs doses of elderly patients are 2/3 from doses for adults patients and 1/2 of cardiac glycosides and diuretics.

3. **Sex.** Young males are more prone to sedation from barbiturates than females. Females are more sensitive to drugs during menstrual cycle, pregnancy. During pregnancy many drugs may provoke abortion, have mutagenic (damage DNA), teratogenic (rise ugliness), embryo toxic (embryo death), faetotoxic (new-born child breath) effects.

4. **Pathological status/disease:** Liver disease decreases the ability to metabolize drugs, while kidney disease hampers the excretion of drugs. Antipyretic

drugs influence only in the case of fever, cardiac glycosides in the case of heart insufficiency.

5. **Functional status:** (e.g. caffeine has greater influence on when a person is tired).

6. **Mass and surface of body.**

7. **Genetic factors.** When glucose 6 dehydrogenase activity was decreased genetically antimalaria drugs e.g. chloroquine sulfas) cause haemolysis.

8. **Circadian rhythm.** Metabolism and action of some drugs follows a diurnal rhythm. The natural factors are temperature, radiation, humidity etc. (e.g. aminazine is more toxic in low temperature).

9. **The anthropogenic factors** are connected with exponent of pollution of surrounding environment (e.g. when a patient takes nitroglycerine and eats water-melon with nitrates a hypotensive crisis may occur).

Drug excretion is the process of elimination of a drug or metabolite from a body. Elimination of drugs from the blood follows exponential (a first-order) kinetics. The elimination process can be saturated after high doses of some drugs and elimination will then follow a zero-order kinetics. Ethanol is a prototypic example. For drugs which are eliminated by a first-order kinetics, the fractional change in the amount of a drug in plasma or blood per unit of time is expressed by the **half-life** ($t_{1/2}$), or by the **elimination rate constant** (k), which is equal to $0.693/t_{1/2}$.

Routes of elimination. A kidney is the most important organ for excretion of drugs. Excretion of drugs and their metabolites into urine involves three processes:

Glomerular filtration. Water-soluble and polar compounds are filtrated under hydrostatic pressure unable to diffuse back into circulation. Drugs dissolved in blood plasma are excreted in this way.

Active tubular secretion. Mechanisms for active tubular secretion exist in the proximal tubule. Drugs such as organic acids (e.g. quinine sulfas) are transported by these systems.

Passive tubular reabsorption is typical for lipophilic nonpolar drugs.

Biliary tract and faeces are important routes of excretion for some drugs

which are metabolized in a liver (e.g. digitoxinum).

Drugs and their metabolites can also be eliminated with expired air, sweat, saliva, tears, and breast milk. Drugs eliminated through these routes tend to be lipid-soluble and nonionized.

Effect of repeated doses. If the time interval between doses is less than four of its half lives a drug accumulates in a body. In this case the total body stores of the drug increase exponentially to a plateau. This plateau is known as a **steady-state concentration**.

PHARMACODYNAMICS

Mechanisms of drug action. Most drugs interact with macromolecular components (called **receptors**) of a cell or an organism to begin biochemical and physiologic changes which causes drugs observed effects, or response, or primary pharmacological reaction. Receptors bind ligands and transduce signals. A drug is called an **agonist** if it interacts with specific receptor, causes its conformation biochemical reactions, produces some of the effects of endogenous compounds. Agonists (e.g. acetylcholine) have intrinsic activity. Intrinsic activity is a drug ability to stimulate receptor and cause specific effects. An **antagonist** is a drug which has no intrinsic activity, even when it can reduce or abolish the effect of an agonist, protect from neuromediators and hormones action. Examples of pure antagonists are atropini sulfas and tubocurarini chloridum, which inhibit the effect of acetylcholine. If antagonists occupy the same receptors as agonists they are called concurrent antagonists (e.g. atropini sulfas). If antagonists occupy other sites of macromolecules which do not belong to a specific receptor they are called nonconcurrent antagonists. Some drugs (e.g. nalorphini hydrochloridum) are agonists-antagonists or synergoantagonists; they have some intrinsic activity and may activate one type of receptors and block another one. There are drugs which may not cause a response by interacting with receptors. These drugs may combine with small molecules or ions found in a body (e.g. chelating agents).

Receptors are specific drug-binding sites in a cell or on its surface, which mediate the action of a drug. Some drugs (e.g. mannitolum) are believed not to have

specific receptors. There are other targets of drugs action as ion channels, enzymes, transport proteins, messengers (G protein etc.), genes. There are different types of receptor binding: covalent, ionic, and Van der Waals bonds. Ion receptors are confined to excitable tissue (e.g. central nervous system - the CNS, neuromuscular junction, autonomic ganglia). Agonists which activate ion channel receptors produce depolarization or hyper polarization. (e.g. nicorandilum activates calcium channels). Examples of ion channel receptors include the nicotinic acetylcholine receptor, a gamma-aminobutyric acid (GABA) receptor, a glutamine receptor, and a glycine receptor. Examples of ion channels blockers are local anesthetics (block sodium channels), nifedipinum (blocks calcium channels).

Certain receptors when exposed to an agonist repeatedly can become desensitized or down-regulated. For example, β -adrenergic bronchodilators used in the treatment of patients with asthma can become less effective over time when administered at the same concentration. Super sensitivity of receptors to agonists can occur with chronic administration of an antagonist. For instance, the abrupt discontinuation of propranolol in a patient who has been taking it constantly could precipitate dysrhythmias. Super sensitivity may result from the synthesis of additional receptors (up-regulation).

Prospects of drug action:

1. Preresorbative action (e.g. lidocainum);
2. Resorbative action (e.g. papaverini hydrochloridum);
3. Reflexive action (e.g. validolum);
4. Main action (e.g. diuretics on diuresis);
5. Direct action (e.g. M-cholinomimetic drugs on M-cholinoreceptors);
6. Indirect action (e.g. after cardiac glycosides influence on a heart and haemodynamics the oedema becomes smaller);
7. Adverse action (e.g. allergic reactions after benzylpenicillinum administration disbiosis including by antibiotics; toxic actions of drugs in the case of overdoses; syndrome of abolition for glucocorticoids; phenomenon of giving effect back in the case of course of antimicrobial drugs treatment is not

observed and there is diseases aggravation. There are also other adverse actions as teratogenic, embriotoxic, phaetotoxic, and carcinogenic influence;

8. specific action (e.g. antivirus drugs influence on virus);
9. nonspecific action (e.g. thiamini bromidum is cardio protector);
10. reversible and nonreversible action (e.g. anticholinesterase drugs that reversible or nonreversible connect the enzyme).

Principles of drugs action: physical (e.g. carbo activatus), physical and chemical (e.g. cardiac glycosides), chemical (e.g. acids), biochemical (e.g. proserinum), concurrent (e.g. sulfonamides).

Types of drug action (as an example of drugs which influence the CNS): sedative, depressing, paralyzing, tonic, and stimulative.

There are different **types of pharmacological reactions of drugs:**

1. Normal reactions when the effect increases with doses that may be expressed as:
 - a) Line dependence (e.g. papaverini hydrochloridum);
 - b) Parabola or hyperbola dependence (e.g. morphini hydrochloridum or sulfonamides);
 - c) S-similar dependence (e.g. adrenalini hydrochloridum).
2. Decreased reactions may be expressed as:
 - a) Tachyphylaxis when the effect decreases if a drug is often administered (e.g. ephedrini hydrochloridum)
 - b) Tolerance when drugs are administered for a long time (e.g. cathartics);
 - c) Drug dependence – psychic (e.g. cocainum), physical (e.g. morphini hydrochloridum);
3. Increased reactions may be expressed as:
 - a) Idiosyncrasy when a reaction of an organism increases genetically (e.g. novocainum);
 - b) Allergy in which an immunological reaction takes place (e.g. benzympenicillinum);
 - c) Sensibility when there are reactions of drugs after protein drugs have been administered in an organism (e.g. serum after enzymes administrative).

When drugs are administered for a long time in combinations **antagonism or synergism** may occur.

There are some **types of antagonism**:

- 1) Physical antagonism (e.g. carbo activatus);
- 2) Chemical antagonism (e.g. acids and alkalines). Two drugs combine with one another for an inactive compound;
- 3) Functional (pharmacologic) antagonism:
 - a) Competitive (direct) antagonism – drugs influence on the same structures (e.g. pilocarpini hydrochloridum and atropini sulfas). Competitive antagonism of drugs is conjugated with effect when agonists interact in a reversible manner for the same agonists receptor sites;
 - b) noncompetitive (indirect) antagonism – drugs influence on different structures and the effect is opposite (e.g. pilocarpini hydrochloridum, adrenalini hydrochloridum). Noncompetitive antagonism binds irreversibly to a receptor site or to another site which inhibits a response to the agonist;
 - c) absolute antagonism is absolute according to all effects (e.g. neodicumarinum, vikasolum);
 - d) non-absolute antagonism – it is realized according to one or several effects (e.g. pilocarpini hydrochloridum, atropini sulfas).

Pharmacologic antagonism occurs when an antagonist prevents an agonist from interacting with its receptors to produce an effect. This type of antagonism can be either competitive or noncompetitive.

Physiologic antagonism. With pharmacologic antagonism, an agonist and antagonist compete for the same receptor site. In contrast to physiologic antagonism, drugs act independently on two different receptors. Physiologic antagonism is exemplified by one drug acting on the sympathetic nervous system causing a heart rate to increase and causing vasoconstriction; while another drug, acting on a parasympathetic nervous system, decreases a heart rate and causes vasodilatation.

Synergism is similar directing action of two or some drugs when their effect is more than that of each component.

There are different **types of synergism**:

1. **Summing or additive synergism** – when pharmacological effect is the sum of the two drugs or more effects (e.g. *caffeinum* + *acidum acetylsalicylicum*);
2. **Synergism, based on potentiation** – when pharmacological effects of two or more drugs are more than the influence of each drug (e.g. *aminazinum* and general anesthetics);
3. **The direct synergism** – which explains drug influence on the same structures (e.g. action of *atropini sulfas* and *homatropini hydrochloridum* on a pupil);
4. **Indirect synergism** – which explains drug influence of the different structures (e.g. action of *atropini sulfas* and *adrenalini hydrochloridum* on the pupil);
5. **Absolute synergism** – which consists of summing all drugs effects (e.g. *captopyrylum* and *hydrochlorthiazidum*);
6. **Non-absolute synergism** – which explains the summing of one or two effects (e.g. *aminazinum* and hypnotics). Prescription of some drugs (polypragmasy) may change the time of pharmacological effect, their expression and duration.

During repeated drugs administration **accumulation** may be observed. The **material accumulation** takes place when a drug substance cumulates in organs and systems (e.g. *phenobarbitalum*). The **functional accumulation** is pharmacological effect of accumulation (e.g. *spiritus aethylicus*). There is a mixed accumulation for cardiac glycosides.

A **therapeutic index** is a ratio used to evaluate the safety and usefulness of a drug for an indication. It is a measurement which describes the relationship between doses of a drug required to produce undesired and desired effects.

The formula for the therapeutic index is:

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

where LD_{50} is a minimum dose which is lethal or toxic for 50% of the population, and ED_{50} is a minimum dose which is effective for 50% of the population. Ideally, the LD_{50} should be a much higher dose than the ED_{50} , so that the therapeutic index would be bigger.

Drugs Affecting Nervous System

Drugs Affecting Peripheral Neurohumoral Transmission

Neurotropic drugs influence the nerve regulation of organism's functions. By means of such medicaments it is possible to influence the neurotransmission of impulses at different levels of the CNS and in the afferent and efferent ways of peripheral innervations. Classification of neurotropic drugs is based on the localization of their action according to their influence on the peripheral or the CNS. There are drugs which influence the efferent and afferent innervations. These are of considerable importance for the physiologic control of the involuntary organs but are directly influenced by only a few drugs.

Drugs, effect on peripheral afferent nervous system

In this group there are local anesthetic agents, adstringentive, mucilaginous, irritative agents.

Local anesthetic agents act by blocking both sensory and motor nerve conduction to produce a temporary loss of sensation without a loss of consciousness. Unlike general anesthetics, they normally do not cause the CNS depression. Structurally all local anesthetics consist of a hydrophilic amino group linked through a connecting group to a lipophilic aromatic residue. If the connecting link between an intermediate group and an aromatic residue is an ester group, the site of metabolism is hydrolysis by plasma pseudocholinesterase. If a link is an amide bond, hydrolysis occurs in the liver. The greater the length of the connecting and amino groups, the greater the potency and the toxicity of local anesthetic. Local anesthesia is the condition which results when sensory transmission from a local area of a body to the CNS is blocked. The local anesthetics constitute a group of chemically similar

agents which block sodium channels of excitable membranes. Because these drugs can be administered locally by topical application or by injection in the target area, the anesthetic effect can be restricted to a localized area, e.g. the cornea or an arm. When given intravenously these drugs have effects on other tissues. Many drugs classified in other groups, e.g. antihistamines and beta-blockers, have significant local anesthetic effects. Local anesthetics are weak bases and, thus, are usually water-insoluble. The drug may be dispensed as a crystal but usually is prepared as an acidic salt solution, which is highly water-soluble and stable.

Pharmacokinetics: Many shorter-acting local anesthetics are readily absorbed into the blood from the injection site after administration. The duration of local action is therefore limited unless a blood flow to the area is reduced. This can be accomplished by administration of a vasoconstrictor (usually an agonist sympathomimetic) with a local anesthetic agent. Cocainum is an important exception to this rule since it has intrinsic sympathomimetic action (because it inhibits norepinephrine reuptake into nerve terminals); cocainum does not require any additional vasoconstrictor. The longer-acting agents, e.g. bupivacainum, are also less dependent on the coadministration of vasoconstrictors. Metabolism of ester local anesthetics is carried out by plasma cholinesterases and may be rapid. The amides are hydrolyzed in the liver and have half-lives from 1.8 hours to 6 hours. Bupivacainum and ropivacainum are very lipid-soluble and long-acting local anesthetics. Liver dysfunction may increase the elimination half-life of amide local anesthetics.

Mechanism of action. Local anesthetics slow down the propagation of nerve impulses by reducing the rate of rise of the action potential and the rate of repolarization. The increased threshold for electrical excitability results in a complete block of conduction. Local anesthetics specifically block nerve conduction by interfering with cell membrane permeability to sodium, particularly voltage-dependent Na^+ channels. The cation forms of local anesthetics appear to bind to specific sites in or near the Na^+ channels, decreases permeability for Ca^{2+} and K^+ .

Specific receptor theory postulates that the local anesthetic displaces Ca^{2+} from a site near the Na^+ channel and then blocks the adjacent Na^+ channel.

Membrane expansion theory hypothesizes that local anesthetics, because of their lipophilic properties, incorporate into the cell membrane, preventing the opening of pores and, thus, interfering with the passage of electrolytes.

Local anesthetics block voltage-dependent sodium channels and reduce the influx of sodium ions, thereby preventing depolarization of the membrane and blocking conduction of the action potential. Local anesthetics gain access to their receptors from cytoplasm or membrane. Since a drug molecule must cross a lipid membrane to reach a cytoplasm, the more lipid-soluble (nonionized, uncharged) form reaches effective intracellular concentrations more rapidly than does the ionized form. On the other hand, once inside the axon, the ionized (charged) form of a drug is the more effective blocking entity. Local anesthetics disturb surface membrane properties and its energy supply. Smaller fibers are blocked more easily than larger ones, and myelinated fibers are blocked more easily than unmyelinated ones. It is thought that activated pain fibers fire rapidly and, that pain sensation may be selectively blocked by these drugs.

Therapeutic uses: Local anesthetics are most commonly used for minor surgical procedures. Local anesthetics are also used in spinal anesthesia and to produce autonomic blockade in ischemic conditions. Slow epidural infusion at low concentrations has been used successfully for postoperative analgesia. Repeated epidural injection in anesthetic doses may lead to tachyphylaxis, however.

The first local anesthetic was **cocainum**. Cocainum is alkaloid. Cocainum is an ester of benzoic acid.

Pharmacokinetics: Cocainum is quickly absorbed across mucosa membranes in gastrointestinal tracts degraded by plasma esterases and has a half-life approximately an hour. Tolerance, abuse, and poisoning can occur with cocainum overuse. Cocaine is metabolized in the blood by ester hydrolysis using pseudocholinesterase.

Pharmacologic CNS effects: Cocainum initially produces euphoria and sometimes dysphoria, blocks neuronal uptake of noradrenaline, connects with dopamine transferents. The initial effect is followed by post stimulatory depression

and drug dependence.

Cardiovascular effects: Cocainum blocks the uptake of catecholamines at adrenergic nerve terminals. This causes sympathetically mediated tachycardia and vasoconstriction leading to hypertension.

Modern local anesthetics are divided into ethers: Novocainum, Dicainum, Anaesthesinum and replaced amides: Lidocainum, Trimecainum, Ultracainum, Bupivacainum, Mepivacainum, Ropivacainum.

Novocainum (procainum) is an ether of diethylaminoethanol and para-aminobenzoic acid (PABA).

Pharmacokinetics: Novocainum is well-absorbed following parenteral administration and is rapidly metabolized by pseudocholinesterase. It has a short duration of action. The drug lacks of topical activity. Novocainum administration causes minimal systemic toxicity and no local irritation. Novocainum has neuroplegic, hypotensive, antiarizthmic and spaspolitic effects, decreases gastric secretion.

Pharmacologic effects, in addition to local anesthetic activity, include a procainum-sulfonamide antagonism. A metabolic product of hydrolysis novocainamiaum is the PABA, which inhibits the action of sulfonamides. Novocainum is available to administer with and without adrenalinum or mesatomum. **Adrenalini hydrochloridum** or **Mesatonum** decrease the rate of anesthetic absorption in the bloodstream and so approximately doubles the duration of anesthesia produced by a given dose.

Dicainum. It is approximately **10 times more potent** (and **more toxic**) than **novocainum**. Solution is used topically on mucous membranes in otolaryngology and ophthalmology.

Anaesthesinum is an ester and derivative of the GABA but is not solved in water. It is used in suppositories in the case of hemorrhoid, in unguenties, liniments, aspersiones locally in dermatology, surgery, and stomatology.

Lidocainum is an amide local anesthetic and an acetanilide derivative.

Pharmacokinetics: Lidocainum is rapidly absorbed after parenteral

administration and is metabolized in the liver by microsomal mixed-function oxidases.

Pharmacologic effects include rapid onset of anesthesia and minimal local irritation - a greater potency and **longer duration of action** than **novocainum**. The major **clinical use** of lidocainum is as a local anesthetic and, intravenously, as an antiarrhythmic agent. Lidocainum can be administered with or without adrenalinum in all types of anesthesia: topical mucosal, nerve block, spinal and caudal. **For topical anesthesia lidocainum is available in the form of** ointment, (gel), cream, solution, spray.

Trimecainum is less active than lidocainum and is used in all types of anesthesia besides topical. It has antiarrhythmic sedative and analgesics action.

Prilocainum like lidocainum and prilocainum is an amide local anesthetic. Its onset and duration of action are slightly longer than those of lidocainum. The major disadvantage of prilocainum is the production of methemoglobinemia and a shift of the oxygen-dissociation curve for hemoglobin to the left. Prilocainum has been used for infiltrative, regional, and spinal anesthesia.

Etidocainum is similar to lidocainum except for its greater potency and longer duration of action. Etidocainum is used clinically for inepidural, infiltrative, and regional anesthesia. The drug usually blocks motor fibers before sensory fibers. Etidocainum hydrochloride is available both with and without adrenalinum.

Mepivacainum like lidocainum is an amide-type local anesthetic. **Pharmacokinetics.** Mepivacainum is similar to lidocainum. However, it does not have antiarrhythmic activity. Mepivacainum is more rapid than lidocainum, and its duration of action is longer. Major uses of mepivacainum are for infiltrative and regional nerve block anesthesia. It also can be used for spinal anesthesia.

Bupivacainum amide local anesthetic is structurally similar to mepivacainum. It is more potent and has a longer duration of action than mepivacainum, the onset of action is slower than that of mepivacainum. Bupivacainum is used mainly for regional nerve block anesthesia.

Ultracainum is an amide, it has a quick and relatively long action. It has low

toxicity, it is not solved in lipids, does not penetrate through hemato-encephalic barrier and placenta, conjugate with protein. It is used in stomatology practice together with adrenalini hydrochloridum (“Ultracainum-D-C”, “Ultracainum-D-C forte”). **Adverse effects:** headache, dyspepsia, and allergic reactions.

Adverse systemic effects of local anesthetics result from absorption of toxic amounts of these agents into the bloodstream. Adding adrenalini hydrochloridum, a vasoconstrictor, to the optimal concentration of a local anesthetic reduces the rate of systemic absorption of the anesthetic and so can decrease systemic toxicity. Seizures, the result of absorption of the local anesthetic and stimulation of the CNS, are the most serious adverse effect. Convulsions, if they occur, are treated with basic supportive measures, including ventilation and oxygenation, and with intravenous diazepam. Respiratory failure secondary to the CNS depression is a late stage of intoxication. A quinidine-like effect on the myocardium can be produced by local anesthetics. Hypotension is a late effect that can occur as the result of myocardial depression and peripheral arterial vasodilatation. Affected patients are treated with appropriate parenteral vasopressor agents. Allergic reactions to local anesthetic agents rarely occur.

	Drug	Drug forms
1.	Dicainum	Pulv.
2.	Anaesthesinum	Pulv.; Tab. 0,3; Ung. 5%
3.	Novocainum	Pulv.; Amp. 0,25%, 0,5% - 1, 2, 5, 10, 20 ml; Amp. 1-2% - 1, 2, 5, 10 ml; Flac. 0,5% - 200, 400 ml; Ung. 5%, 10%; Supp. rect. 0,1
4.	Trimecainum	Pulv.; Amp. 0,25% - 10 ml 0,5% - 2, 5, 10 ml 1% - 2, 5, 10 ml 2% - 1, 2, 5, 10 ml 5% - 1, 2ml

5.	Lidocainum	Amp. 1% - 10 ml, 20 ml 2% - 2 ml, 10 ml 10% - 2 ml
6.	Ultracainum	Amp. 2, ml; Flac. 20 ml
7.	Bupivocainum	Sol. 0,25% 20 ml

Astringent drugs

These drugs are divided into organic (Tanninum, flores Chamomillae, cortex Quercus, fructus Myrtilli, folia Salviae, herba Hyperici) and non-organic (Alumen, Bismuthi subnitras and salts of heavy metals in low concentrations). **Mechanism of actions:** The drugs coagulate mucous surface layer with albuminate forming, which protect nerve endings from irritating. **Pharmacological effects:** They have anesthetic effect, cause local vasoconstriction, decreasing of permeability and inflammatory. **Therapeutic uses:** inflammatory diseases of the mucous and skin, burns, poisoning, enteritis and colitis.

Adsorbents

There are Carbo activatus and Enterosgel which are absorbing chemical materials on their surface. Enterosgel connects microorganisms, restores intestines flora, and has immunomodulate action. They protect nerve endings, prevent poisons suction. **Therapeutic uses:** Inflammatory diseases of the GI tract, poisoning, meteorism, and diarrhea.

Mucosal drugs

Amylum, Semina Lini and components of Almagel have covering action. **Mechanism of action;** These drugs interact with H₂O and form colloid solutions, which cover mucous. **Pharmacological effects:** They are decreasing irritation of nerve endings and suction of poisons. **Therapeutic uses:** Inflammatory diseases of the GI tract, poisoning, meteorism, and diarrhea.

Irritating drugs

Mentholum, Oleum Terebinthinae rectificatum, Solutio Ammonii caustici, Succus Sinapsimus are irritating sensitive nerve endings of the skin and mucos.

The main effects are local (exudation, hyperemia etc.), reflex stimulation of breathing and cardiovascular centers, improvement of tissues blood supply and troficity by stimulation of the corresponding segments of a spinal cord, analgetic effect connecting with endorphine and encefaline release. Mentholum is contained in validolum, which is used in angina pectoris, has a spasmolitic effect. It is used in oils for nose because may constrict vessels and decrease secretion. Oleum Terebinthine rectificatum is used in neuralgia, mialgia, and arthralgia. Sol. Ammonii caustici is used for breathing stimulation, for vomiting, in the case of alcoholic intoxication, for the washing of surgeon hands. Succus Sinapsimus, emplastrum capsici are used in myositis, neuralgia, and respiratory organs diseases.

	Drug	Drug forms
1.	Tanninum	Pulv.
2.	Decoctum Corticis Quercus	1:5; 1:10
3.	Infusum Folium Salviae	Infusum 1:10, 1:5
4.	Infusum Flores Chamomillae	Infusum 1:10, 1:5
5.	Infusum Folium Hyperici	Infusum 1:20, 1:10
6.	Bismuthi subnitras	Pulv.; Ung. 10%
7.	Oleum Terebinthinae rectificatum	Flac. 50 ml
8.	Mentholum	Pulv.; Oleum Mentholi 1%, 2%; Sol. spirit. 1%, 2%
	Solutio Ammonii caustici	Flac. 10, 40, 100 ml; Amp. 1 ml
	Sinapsimus	Ad usum externum
	Mucilago Amyli	Ad usum internum

	Semen Lini	Ad usum internum
	Carbo activatus	Pulv.; Tab. 0,25, 0,5
	Enterogel	Pulv. 45, 135, 225, 450, 650, 900

Drugs effect on peripheral efferent nervous system

The peripheral efferent nervous system consists of somatic and autonomic nervous systems.

Parasympathetic nervous system. Innervation of organs: The parasympathetic nervous system innervates the heart, bronchial smooth muscle, iris, salivary glands, and urinary bladder. Under normal conditions, the heart, eye, gastrointestinal tract, urinary bladder, bronchi, and salivary glands are under parasympathetic control.

Sympathetic nervous system

Location of preganglionic neurons: in the sympathetic (thoracolumbar) nervous system, the neurons are located in lumbar and thoracic portions of the spinal cord. **Location of ganglia:** in the sympathetic nervous system, the ganglia are close to a spinal cord, so that preganglionic axons are short and postganglionic axons are long. **Neurotransmitters:** these chemical mediators transmit nerve impulses across junctions such as synapses. At **ganglionic synapse** in both sympathetic and parasympathetic nervous systems, the neurotransmitter is **acetylcholine**. The two systems differ at postganglionic synapse. A **parasympathetic** neurotransmitter is **acetylcholine**. A **sympathetic** transmitter is usually **noradrenaline (NE)**, but at sweat glands and at some blood vessels, it is **acetylcholine**. **Dopamine** is an important vasodilator transmitter in renal blood vessels. Dopamine and the NE are released from their nerve endings by the same mechanism responsible for the ACh release. Termination of action, however, is quite different. Metabolism is not responsible for termination of action of catecholamine transmitters, noradrenaline and dopamine. Instead, diffusion and reuptake (especially uptake) reduce their concentration in a

synaptic cleft and stop their action. Outside the cleft, these transmitters can be metabolized – by monoamine oxidase (MAO) in cytosol and catechol-o-methyltransferase (COMT) and the products of these enzymatic reactions are excreted. Transport back into the noradrenergic neuron followed by either vesicular storage or by enzymatic inactivation by the MAO.

Cholinergic receptors are broadly subdivided into **muscarinic** and **nicotinic receptors**. **Muscarinic receptors** are further subdivided into M_1 , M_2 , M_3 , M_4 , M_5 receptors. Muscarinic receptors M_1 are found in the CNS. In addition, M_1 receptors are also found at autonomic ganglia; M_2 receptors are situated on myocardium. M_3 receptors are found in the glands, M_4 receptors – in the smooth muscles, M_5 receptors – in the noninnervated tissues. One involves G protein coupling of muscarinic receptors (especially M_1 and M_3 receptors) to phospholipase C, a membrane-bound enzyme, leading to the release of the second messengers diacylglycerol (DAG) and inositol - 1, 4, 5-trisphosphate (IP_3). The DAG modulates the action of protein kinase C, an enzyme important in secretion, while IP_3 evokes the release of calcium from intracellular storage sites, which results in contraction. The second mechanism couples muscarinic receptors (especially M_2 receptors) to adenylylcyclase through the inhibitory G_i coupling protein. The third mechanism couples the same receptors directly to potassium channels in the heart and elsewhere; muscarinic agonists facilitate opening of these channels. Muscarine is a classic agonist for muscarinic receptors and atropine is an antagonist. **Nicotinic receptors** are found in the CNS, in autonomic ganglia, and in striated muscle. They are divided into N_1 , N_2 , N_3 -cholinoreceptors. N_1 - and N_2 -cholinoreceptors are localized in the CNS, N_1 -cholinoreceptors – in ganglia, N_2 -cholinoreceptors – in muscular synapses, N_3 -cholinoreceptors – in the adrenal glands. The mechanism of nicotinic action has been clearly defined. The ACh receptor is located on a channel protein that is selective for sodium and potassium. When a receptor is activated, the channel opens and depolarization of the cell occurs as a direct result of the influx of sodium. Nicotine, a classic agonist, first stimulates and then blocks autonomic ganglia and skeletal muscle end-plates. **Adrenergic receptors** - for norepinephrine (noradrenalin) and epinephrine (adrenalin) are also of several types.

α -Adrenergic receptors. Some α -adrenergic receptors precede the synapse between nerve terminal and effector organ; others are postsynaptic. **α_1 -Adrenergic receptors** are **postsynaptic**. They are found on blood vessels, on the radial muscle of the eye, in the gastrointestinal tract, and on the splenic capsule. **α_2 -Adrenergic receptors** are **presynaptic** or **postsynaptic**; all seem to serve an inhibitory function. Isoproterenol is ineffective on α_2 receptors. **Presynaptic α_2 receptors** are found at adrenergic and cholinergic nerve terminals. Presynaptic α_2 receptors, when activated, inhibit the release of further neurotransmitter. **Postsynaptic α_2 receptors** are found in blood vessels and in the CNS.

β -adrenergic receptors. **β_1 -adrenergic receptors** are found predominantly on cells in the heart and intestine. **β_2 -adrenergic receptors** are found on bronchial, vascular and uterine smooth muscle. **β_3 -adrenergic receptors** are localized in adipose cells.

Direct effects of autonomic stimulation on various organs. Stimulation of effector organs may be either direct or indirect. A **direct** effect occurs when the nerve innervating an organ is stimulated. **Indirect** responses are mediated by changes caused in other organs.

Drugs effecting on neurohumoral transmission

1. Drugs can affect neurohumoral transmission at various steps. They can affect:

- a. Synthesis, storage, or release of a neurotransmitter
- b. Interaction between transmitter and receptor
- c. Enzymatic destruction of a neurotransmitter
- d. Transport of a transmitter into cells
- e. Recovery of a cell membrane after a transmitter-receptor interaction

2. Adrenergic drugs are divided into:

- 1) Adrenomimetic drugs;
- 2) Antiadrenergic drugs;

ADRENOMIMETIC AGENTS.

These are drugs which mimic the actions of the sympathetic nervous system. Adrenomimetic drugs are divided into medicaments of a direct and indirect action. Adrenomimetic drugs of direct action sensitize adrenoreceptors similar to mediator directly. They include:

1) α, β -adrenomimetic drugs – adrenalini hydrochloridum, noradrenalini hydrotartas.

2) α -adrenomimetic drugs:

α_1 (mainly) - mesatonum

α_2 (mainly) – xylomethazolinum, naphthyzinum.

3) β -adrenomimetic:

$\beta_1 \beta_2$ –isadrinum, orciprenalini sulfas

β_1 - dobutaminum

β_2 –salbutamolum, fenoterolum.

Adrenomimetic drugs of indirect action (sympathomimetic) may release mediators from labil vesicles, brake the reuptake, inhibit the MAO and increase sensitivity of adrenoreceptors to mediators.

Ephedrini hydrochloridum belongs to adrenomimetic drugs of indirect action.

Pharmacokinetics: The drugs similar to endogenous adrenoceptor agonists (adrenalini hydrochloridum, noradrenalini hydrotartras, and dopaminum) rapidly metabolized by the COMT and MAO. As a result, these adrenoceptor agonists are inactive when administered enterally. These agonists have a short duration of action. When administered parenterally, they do not enter the CNS in significant amounts. Isadrinum, a synthetic catecholamine, is similar to endogenous transmitters but is not readily taken up into the nerve ending. Mesatonum is resistant to the MAO and COMT. These agents are orally active; they enter the CNS, and their effects last

much longer than do those of catecholamines.

Adrenalini hydrochloridum (epinephrine)

Pharmacokinetics Absorption is poor with oral administration because the drugs are rapidly conjugated and oxidized. Absorption is slow with subcutaneous administration (duration of action 30 minutes) because the drugs cause local vasoconstriction. It may be administered also intramuscularly. The drug can be given intravenously (duration of action 5 minutes), but this route must be used with caution so that the heart does not fibrillate. The drug may be administered into heart with caution on the background of atropine sulfate. The liver is important in the degradation of adrenalinum. The majority of the dose is metabolized by catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO), and the metabolites and some of nonmetabolized adrenalinum are excreted in the urine.

Pharmacologic Effects: Adrenalini hydrochloridum interacts strongly with both β and α receptors. Its effects on some body systems depend on the concentration of adrenalinum as well as on the type of a receptor. At low concentrations, β effects predominate, and at high concentrations, α effects predominate.

Mechanisms of Action: **Alpha₁ receptor effects:** Alpha₁ receptor effects are mediated primarily by the coupling protein G_q, which leads to activation of the phosphoinositide cascade and the release of inositol-1, 4, 5-trisphosphate (IP₃) and diacylglycerol (DAG) from membrane lipids. Calcium is subsequently released from stores in smooth muscle cells, and enzymes are activated. Direct gating of calcium channels may also play a role in increasing intracellular calcium concentration. **Alpha₂ receptor effects:** Alpha₂ receptor activation results in inhibition of adenylylcyclase via the coupling protein G_i. **Beta receptor effects:** Beta receptors (β_1 , β_2 , and β_3) stimulate adenylylcyclase via the coupling protein G_s, which leads to an increase in cAMP concentration in the cell. Effect on the CNS is weak, such as headache, nausea, and fibrillations of skeletal muscles.

Effects on blood pressure. A large dose of adrenalinum hydrochloridum, administered intravenously, causes an increase in blood pressure, the systolic

pressure increasing more than the diastolic. Subsequently, the mean pressure falls below normal before returning to the control value. The first rise in pressure is due to ventricular contraction through activation of β_1 -receptors, then there is the decrease of pressure by stimulation centre of pneumogastric nerve. The second rise of pressure is connected with vasoconstriction through activation of α_1 -receptors. An initial increase in heart rate, which, at the height of the vasopressor response, will be slowed by a compensatory vagal discharge. Then the pressure may decrease because of β_2 -adrenoreceptors stimulation. Low doses also cause a fall in blood pressure because the β_2 (vasodilator) receptors are more sensitive to adrenalini hydrochloridum than the α (vasoconstrictor) receptors.

Vascular effects. Adrenalini hydrochloridum exerts its action on small arterioles and precapillary sphincters. It may delay coronar, brain and skeletal muscles vessels and constrict cutaneous and peritoneal vessels. Its vascular effects include a decreased cutaneous blood flow; an increased blood flow to skeletal muscle at low concentrations, and a decreased flow at higher concentrations; an increased hepatic blood flow with increased splanchnic vascular resistance; an increased renal vascular resistance, producing a decreased renal blood flow; an increased arterial and venous pulmonary pressure; an increased coronary blood flow, caused indirectly by an increase in the work of the heart and mediated by local effectors.

Effects on the heart produced by adrenalini hydrochloridum include: a direct effect on β_1 , receptors, producing a slight initial increase in heart rate, which is slowed down by a compensatory vagal discharge; increased stroke volume; increased cardiac output. These effects are connected with an adenylcyclase activation, increase of cAMP level, glycolysis, glycogenolysis, lipolysis activation; and may cause arrhythmias.

Effects on smooth muscle depend on the predominant type of adrenergic receptor in the muscle. Adrenalini hydrochloridum relaxes gastrointestinal smooth muscle (α_2 and β -receptor stimulation), while it usually increases sphincter contraction (α stimulation). Uterine contractions may be inhibited (β) or stimulated

(α), depending on menstrual phase or state of gestation. In the bladder, a detrusor muscle relaxes (β), while a trigone and a sphincter contract (α). Bronchiolar smooth muscle relaxes (β_2).

Metabolic effects of adrenalini hydrochloridum also depend on the type of adrenergic receptor. These effects include: an increase in glucose and lactate production via liver and muscle glycogenolysis (β_2); inhibition of insulin secretion (α); an increase in free fatty acids, mediated by cyclic adenosine 3', 5'-monophosphate [cyclic AMP] (β_1); an increase in oxygen consumption; antiallergic effects is connected with decrease of histamine level

Effects on eyes: adrenalini hydrochloridum produces mydriases, reduces intraocular pressure in patients with open-angle glaucoma.

Pharmacologic effects of noradrenalini hydrotartras (norepinephrine). An intravenous infusion raises both systolic and diastolic pressure by constriction of vascular smooth muscle (α receptors) more than adrenalini hydrochloridum. The increased peripheral vascular resistance produces a compensatory vagal reflex which slows the heart rate. Cardiac output may actually decrease although a coronary blood flow is increased. The drug has less effects on metabolism and intestines, does not influence bronchus.

Therapeutic uses: Adrenalini hydrochloridum is used: to treat bronchospasm; for relief of hypersensitivity reactions; it is the primary treatment for anaphylactic shock; to prolong the duration of infiltrative anesthesia; to restore cardiac activity in cardiac arrest; to facilitate aqueous drainage in chronic open-angle glaucoma. Noradrenalini hydrotartras is used for treating hypotension during anesthesia when tissue perfusion is good, and in other status with hypotension and shock.

Adverse effects: Both adrenalini hydrochloridum and noradrenalini hydrotartras can cause: anxiety, headache, cerebral hemorrhage from the vasopressor effects, cardiac arrhythmias, especially in the presence of digitalis and certain anesthetic agents, pulmonary edema from pulmonary hypertension, hypertension.

Isadrinum (isoproterenol)

Pharmacokinetics. Absorption of orally administered isadrinum is unreliable, it is given sublingually. It is readily absorbed when given parenterally or as an inhaled aerosol. It is principally metabolized by the COMT; the MAO plays a much smaller role than in adrenalini hydrochloridum or noradrenalini hydrotartas metabolism.

Pharmacologic effects: Isadrinum has an *N*-alkyl substitution, which makes it act almost entirely on β receptors and has very little effect on α receptors. Intravenous infusion produces a reduction of peripheral vascular resistance in skeletal muscles and in renal and mesenteric vascular beds. Diastolic blood pressure falls down, but owing to an increased venous return, positive inotropic, and chronotropic effects, cardiac output is increased. Systolic blood pressure may increase, but mean pressure decreases. Renal blood flow decreases in normotensive individuals, but it increases in patients with nonhemorrhagic shock. Relaxation of both bronchial and gastrointestinal smooth muscle occurs. A release of free fatty acids occurs; hyperglycemia is less than with adrenalini hydrochloridum. Pancreatic islet cells are activated, stimulating insulin secretion.

Therapeutic uses: Isadrinum is used as a bronchodilator and more often as a cardiac stimulant.

Adverse effects: These are similar to the adverse effects of adrenalini hydrochloridum. Overdosage by inhalation can induce fatal ventricular arrhythmias. Tolerance to the desired effects occurs with overuse in the asthmatic.

Orciprenalini sulfas (Alupent) influences more expressively β_2 -adrenoreceptors. The drug decrease arterial pressure and produces tachycardia less than isadrinum. It is used as a bronchodilatator

Dopaminum. Dopaminum is an intermediate in the synthesis of noradrenalinum.

Pharmacokinetics. Dopaminum resembles adrenalini hydrochloridum and noradrenalini hydrotartras in its pharmacokinetics.

Central dopamine receptors (D₁, D₂, D₃)

a. The central **D₁** receptor site is excitatory and directly activates the adenylate

cyclase system.

b. The **D₂** receptor site is inhibitory in some brain tissues and uses cAMP as its intracellular messenger. Pituitary-related side effects of neuroleptics are thought to be mediated through **D₂** receptors in the pituitary.

c. The **D₃** receptor is localized in the limbic system and is not found in the pituitary. It is principally associated with emotional and cognitive behavior.

Pharmacologic effects

Dopaminum receptor effects: Dopaminum **D₁** receptors activate adenylyl cyclase in neurons and vascular smooth muscle. Dopaminum **D₂** receptors are more important in the brain but probably also play a significant role as presynaptic receptors on peripheral nerves. Dopaminum is an important neurotransmitter in the CNS. It is a direct agonist, acting on β_1 receptors. It also releases noradrenalinum from nerve terminals. The result is a positive inotropic effect on the myocardium. Low or intermediate doses of dopamine reduce arterial resistance in the mesentery and kidney; this raises the glomerular filtration rate. The effect is mediated by a receptor for dopaminum. Dopaminum increases systole pressure but has little effect on diastolic pressure. At higher doses, it acts on α receptors and causes vasoconstriction with a consequent reduction in renal function.

Therapeutic uses: Dopaminum is used in the treatment of cardiogenic and septic shock and in chronic refractory congestive heart failure.

Adverse effects: Overdosage results in excessive sympathomimetic activity. Anginal pain, arrhythmias, nausea, and hypertension can occur, but these effects are short-lived because of dopamine rapid metabolism.

Dobutaminum

Pharmacokinetics: Dobutaminum is not absorbed when given orally. It has a half-life of 2 minutes when given by intravenous injection.

Pharmacologic effects: Though dobutaminum resembles dopaminum chemically, it is a direct β_1 -receptor agonist. It has a greater inotropic than chronotropic effect. Dobutaminum does not act on dopaminergic receptors.

Therapeutic uses: Dobutaminum is used to improve myocardial function in congestive heart failure. Oxygen demands are less than with other sympathetic agonists because dobutaminum causes minimal changes in heart rate and systolic pressure.

Adverse effects: Dobutaminum increases atrioventricular conduction and must, therefore, be used with caution in atrial fibrillation. Other adverse effects are similar to those of other catecholamines.

Mesatonum (phenylephrine)

Pharmacologic effects: Mesatonum has one hydroxyl group in the aromatic ring, practically is not destroyed when administered orally. Mesatonum is a direct-acting synthetic sympathomimetic agent. Its effects are similar to those of noradrenalinum mainly on α_1 -adrenoreceptors, but it is less potent and has a longer duration of action, it decrease intra-ocular pressure also in oper-angular glaucoma. Vasoconstriction, increased atrial pressure, and reflex bradycardia occur with parenteral administration.

Therapeutic uses: Phenylephrine is used: as a nasal decongestant, as a presser agent, to provide local vasoconstriction as an adjunct for use with local anesthetics, in ophthalmology as mydriatic agent.

Adverse effects: Large doses cause cardiac irregularities. Ophthalmic solutions, like intranasal solutions, can be systemically absorbed. Their use in patients taking β blockers increases the risk of cardiac irregularities, myocardial infarction, and intracranial hemorrhage. Rebound nasal congestion can occur with chronic use as a nasal decongestant.

Xylomethazolinum and naphthyzinum influence mainly α_2 adrenoreceptors and are used in the case of rhinitis.

Ephedrini hydrochloridum

Pharmacokinetics: Ephedrini hydrochloridum is absorbed when taken orally. It is resistant to the COMT and MAO, so that its action is prolonged.

Pharmacologic effects: Ephedrini hydrochloridum is a sympathomimetic

agent, that is, it has an indirect action. Its primary action is indirect: it causes the release of noradrenalin from storage in nerve terminals, apparently by competing with noradrenalin for transport into the granules. It also increases sensitivity of adrenergic receptors. When administered intravenously its action is similar to that of adrenalin hydrochloridum. Its pressor response occurs more slowly and lasts 10 times longer. Its potency is 1/250 that of adrenalin hydrochloridum in producing an equivalent pressor response. Ephedrini hydrochloridum increases arterial pressure by causing peripheral vasoconstriction and cardiac stimulation. Its effects on the bronchi and other smooth muscle are qualitatively similar to those of adrenalin hydrochloridum. It causes CNS stimulation, which can result in effects such as insomnia, nervousness, nausea, and agitation. Tachyphylaxis occurs with a repeated administration.

Therapeutic uses: Ephedrini hydrochloridum is used very seldom: in the treatment of bronchial asthma; as a pressor agent in spinal anesthesia for collapse prophylaxis.

Adverse effects: These are similar to the adverse effects seen with adrenalin hydrochloridum. In addition, the CNS effects may occur. Ephedrini hydrochloridum must be used with caution in patients with cardiovascular disease or hyperthyroidism because it is a powerful heart stimulator. Ephedrini hydrochloridum causes a drug dependence.

Phenaminum (Amphetamine)

Pharmacologic effects: Amphetamine acts indirectly by releasing noradrenalin. Amphetamine is also a CNS stimulant. The dextrorotatory (*d*-) form is more active in the CNS than the levorotatory (*l*-) form. Amphetamine depresses the appetite, decreasing food intake, by affecting the feeding centre in the lateral hypothalamus. It increases metabolism to a small extent. Amphetamine is not used because of psychic and physical dependence.

β_2 -Stimulating bronchodilators (salbutamolum (ventolin), fenoterolum (berotek), terbutalinum (bricanil) and others)

Pharmacologic effects: The adrenergic agents which are primarily β_2 agonists

have a relaxing effect on bronchial smooth muscle and show little effect on cardiac β_1 receptors. They also have tocolytic effects duration of their action 2-5 hours.

Therapeutic uses: These agents are used therapeutically for the treatment of bronchial asthma or bronchospasm where their lack of cardiac stimulation is a decided advantage. They are used chiefly as aerosol inhalants. Oral and injectable forms are also available. Salmeterolum (Serevent), Formoterolum (Foradyl), and Clenbuterolum act for 12 hours and are used for protection bronchospasm.

Adverse effects of the β_2 agonists are similar to those seen with the sympathomimetic drugs listed above. Even though their effects are primarily bronchial, they should be used with caution in patients with cardiovascular disease or hyperthyroidism because they can still stimulate (though minimally) β_1 receptors of the heart.

ANTIADRENERGIC DRUGS

Antiadrenergic drug are divided into **sympatholytics**, **antiadrenergic** and **antiadrenergic blocking agents**. Antiadrenergic blocking agents are classified into:

- a. α -adrenergic blocking agents;
- b. β -adrenergic blocking agents;
- c. α - β -adrenergic blocking agents.

α -adrenergic blocking agents may be:

- a. $\alpha_1\alpha_2$ -adrenergic blocking agents – phentolaminum, pyrroxanum, dehydrate ergot alkaloids.
- b. α_1 -adrenergic blocking agents – prazosinum, doxazosinum, terazosinum.

α -adrenergic blocking agents (α blockers)

Phentolaminum and pyrroxanum act by a reversible α -adrenergic blockade.

Pharmacologic effects: These agents produce vasodilation connected with blocking α_1 -postsynaptic adrenoreceptors and reflex cardiac stimulation α_2 -presynaptic adrenoreceptors. They decrease peripheral resistance and increase venous capacity. Both stimulate salivary, lacrimal, pancreatic, and respiratory tract

secretions. They cause a gastric secretion that resembles the effect of histamine. Pyroxanum influences diencephalic part. Pyroxanum is absorbed when given orally and is rapidly excreted by the kidneys; phentolaminum is excreted more slowly. Both can be given parenterally.

Therapeutic uses: Phentolaminum has been used to control acute hypertensive episodes due to pheochromocytoma. In the past phentolaminum was used as a diagnostic test for pheochromocytoma, but it has been replaced by assays for urinary catecholamines. Pyroxanum can be used in the treatment of hypertension in the case of hypothalamic (diencephalic) damages. Phentolaminum has been used in the treatment of Raynaud's phenomenon.

Adverse effects: Both drugs can cause cardiac stimulation, leading to arrhythmias and anginal pain, especially after parenteral administration; they must be used with caution in patients with coronary artery disease. Tolazoline can produce a paradoxical hypertension. Because they induce gastrointestinal stimulation, both drugs must be used with caution in patients with peptic ulcer disease.

Prazosinum is a selective blocker of postsynaptic α_1 receptors, producing vasodilation.

Pharmacologic effects: Prazosinum reduces vascular tone in both resistance and capacitance vessels. It also block phosphodiesterase activity. Because prazosinum has no effect on α_2 receptors, neurotransmitter feedback inhibition is maintained, so that prazosinum causes only a small degree of tachycardia. It decreases arterial pressure with little change in a cardiac output, the heart rate, and right atrial pressure. It may be tachycardia. Prasosinum block α_{2A} receptors of urethra, urine bladder, and prostate. Prasosinum reduces symptoms of obstruction and urinary urgency. Prasosinum is used in arterial hypertension and prostate hyperplasia. Doxazosinum (Cardura), Terazosinum (Kornam) act 24 hours and have the same actions and use. Tamsulosinum (Omnic) – α_1 -adrenoblocker is used in urology only.

Dehydrated ergot alkaloids (dihydroergotaminum, dihydroergotoxinum, dihydroergocristinum).

Mechanism of action: These agents are α -adrenergic blockers as well as being serotonin agonists.

Pharmacologic effects: Dehydrated ergot alkaloids have sedative, antiemetic effect; they widen arteries and narrow veins. They are used in the cases of vestibular disturbances in the air and sea diseases. They directly stimulate smooth muscle of brain vessels, acting on serotonin receptors are used in migraine.

β -Adrenergic blocking agents (β blockers) are divided into selective and nonselective drugs, the drugs with and without sympathomimetic activity.

Drug

β -Blocking Selectivity

Labetololum	Nonselective β - and selective α_1 -blocking activity
Carvedilolum	Nonselective β - and selective α_1 -blocking activity
Nadololum	Nonselective
Pindololum	Nonselective intrinsic sympathomimetic
Propranololum	Nonselective
Timololum	Nonselective
Acebutololum	β_1 -selective, intrinsic sympathomimetic
Esmololum	β_1 -selective, intrinsic sympathomimetic
Celiprololum	β_1 -selective, intrinsic sympathomimetic, β_2 -agonist
Talinololum	β_1 -selective, intrinsic sympathomimetic
Atenololum	β_1 -selective
Betaxololum	B_1 -selective
Metoprololum	B_1 -selective
Bisoprololum	B_1 -selective
Nebivololum	β_1 -selective

Propranololum (anaprilinum) is a nonselective β -antagonist. It competes for both β_1 - and β_2 -receptors.

Pharmacokinetics: Although propranololum is completely absorbed from the gastrointestinal tract, a large portion of the drug is extracted by the liver before it enters the systemic circulation. Wide variation in the hepatic metabolism of the drug among individuals causes significant differences in plasma concentrations attained. Propranololum is approximately 90% bound to plasma proteins. The elimination half time is approximately 3 hours for a small dose, but it is prolonged with larger doses and is significantly prolonged in the presence of cirrhosis. A metabolic product, 4-hydroxypropranolol is active but has a short half-life.

Pharmacologic effects: Propranololum decreases the heart rate and cardiac output and prolongs systole, has membranostabilising action. It decreases total

coronary blood flow and oxygen consumption. It reduces a blood flow to most tissues except the brain.

The antihypertensive effect of propranolol is slow to develop. Propranolol inhibits the renal secretion of rennin. It depresses sodium (Na^+) excretion because it alters renal hemodynamics, an effect that is secondary to the decrease in cardiac output. Propranolol increases airway resistance by β_2 blockade. Since most of the effects of catecholamines on carbohydrate and fat metabolism are mediated by β receptors, propranolol will interfere these events. Propranolol has sedative effect. Propranolol increases the contractility of bronchial, intestinal, and uterine smooth muscles. Propranolol decreases intraocular pressure in open-angle glaucoma.

Therapeutic uses: Propranolol is used for treatment of hypertension, often in combination with a diuretic; Prophylaxis of angina pectoris; Prophylaxis of supraventricular and ventricular arrhythmias. Long-term prophylaxis in patients who have had a myocardial infarction and are at high risk for infarction or sudden death. Management of hypertrophic obstructive cardiomyopathies to reduce the force of myocardial contractions. Management of hyperthyroidism and anxiety states to decrease the heart rate. Prophylaxis of migraine headaches.

Adverse effects and precautions: Propranolol can induce heart failure, especially in patients with compromised myocardial function. Rapid withdrawal can lead to "super sensitivity" of β -adrenergic receptors, which can provoke anginal attacks, arrhythmias, or myocardial infarction. Because propranolol increases airway resistance, it must be used with caution in asthmatics. Because of its effects on carbohydrate metabolism, the hypoglycemic action of insulin may be augmented. Therefore, diabetics being treated with insulin and persons prone to hypoglycemia must use propranolol with caution. Rash, fever, and purpura are characteristic of an allergic response and require discontinuation of the drug. Prolonged use may cause fatigue, depression, nightmares, sexual dysfunction, and peripheral arterial insufficiency. Because of its effects on a peripheral blood flow, propranolol is

contraindicated in patients with Raynaud's phenomenon and other peripheral vessels disorders.

Timololum is a nonselective β -adrenergic antagonist which is 5-10 times more potent than propranolol. Timololum lowers intraocular pressure by reducing the production of aqueous humor; the mechanism is not clear. It does not change the size of the pupil, and vision is not affected. Timololum, in the form of eye drops, is, therefore, useful in the treatment of glaucoma.

Nadololum is a nonselective β -adrenergic blocking agent which is not metabolized and is excreted unchanged in the urine. Its effect and adverse reactions are similar to those of propranololum, but its influence is longer. The introductions are the same as propranololum.

Labetalolum is a nonselective β -adrenoblocker, which has also α_1 -adrenoblocking activity. It is used in the treatment of mild to severe hypertension. Labetalolum reduces peripheral vascular resistance while preventing reflex tachycardia. It can be given intravenously in hypertensive emergencies. Labetalolum may cause postural hypotension and jaundice in addition to the adverse effects seen with other β -adrenoblockers. In contrast to labetalolum α,β -adrenoblocking agent Carvedilolum has such pharmacological properties and also antioxidant action, may be used also in congestive heart failure.

Pindololum is a nonselective β -adrenoblocker, which also has some degree of intrinsic sympathomimetic (α -adrenergic) activity. Unlike the case with propranololum, no rebound tachycardia occurs upon abrupt withdrawal of pindololum. It is used in arterial hypertension.

Acebutololum is a β -adrenoblocker with mild intrinsic sympathomimetic activity (ISA). Its β_1 -adrenoblocking effects exceed its β_2 -adrenoblocking effects. Because of its ISA, it may not cause as slow a bradycardia as propranololum does. It is used for hypertension treatment. Talinololum has the same effects and indications.

Esmololum has short duration of action and intrinsic sympathomimetic activity. It is used more often during operations.

Celiprololum blocks β_1 -adrenoreceptors and stimulates β_2 -adrenoreceptors. It may be used in patients with bronchial asthma and arterial hypertension.

Metoprololum is a selective β_1 -adrenergic antagonist.

Pharmacologic effects: Metoprololum inhibits the inotropic and chronotropic cardiac responses, penetrates through haemato-encephalic barrier. It is 1/50 as potent as propranololum in inhibiting a vasodilator response to isadrinum; however, it is long acting, has membranostabilising action. It is absorbed well when given orally. It is used for treatment arterial hypertension, supraventricular, ventricular arhythmias, ischaemic heart disease.

Therapeutic uses: Metoprololum is used chiefly in the treatment of hypertension, angina pectoris, subventricular and ventricular arrhythmias.

Adverse effects: Metoprololum produces fewer deleterious effects in asthmatic patients because of its selective β_1 -adrenergic antagonism, but its use in asthmatics still requires caution. Other adverse effects are similar to those of propranolol.

Atenololum is a selective β_1 -adrenergic antagonist, hydrophilic, which is administered two times a day and does not influence the CNS.

Betaxololum is a selective β_1 -adrenergic antagonist, which is administered once a day. It is more lipophilic than atenololum. It is also available as a topical formulation for the treatment of glaucoma.

Bisoprololum is a selective β_1 -adrenoblocking agent with long duration of action. It may be used in arterial hypertension and congestive heart failure.

Nebivololum has own vasodilative properties by means of ability to influence the synthesis of NO.

Agents which inhibit the action of adrenergic nerves (sympatholytics)

Reserpinum

Mechanism of action: Reserpinum, a rauwolfia alkaloid, acts via catecholamine depletion. It inhibits the uptake of noradrenalinum into vesicles, and

intraneuronal degradation of noradrenalinum by MAO then occurs. It impairs then restores and synthesis of catecholamines, their connection with ATP in vesicles. This action takes place both centrally and peripherally.

Pharmacologic effects: Blood pressure decreases, which usually triggers reflex tachycardia in normal people through sympathetic stimulation. However, because sympathetic stores are depleted, bradycardia may ensue in people taking reserpinum. Sedation and neuroleptic effect often result, owing to the depleted stores of catecholamines and serotonin (5-hydroxytryptamine, 5-HT) in the brain. Vagotonic effects on gastrointestinal tract.

Therapeutic uses: The major therapeutic use of reserpinum is in the treatment of hypertension.

Adverse effects: sedation, psychic depression that may result in suicide, abdominal cramps and diarrhea, gastrointestinal ulceration, possible increased incidence of breast carcinoma

Raunatinum is the sum of rauwolfia alkaloids and novogalenic drug, and is used for hypertension treatment.

Octadinum (Guanethidine)

Mechanism of action: Octadinum acts presynaptically and is a peripheral sympatholytic agent. It impairs the response to sympathetic stimulation by inhibiting the release of neurotransmitters from peripheral adrenergic neurons. Octadinum is taken up by adrenergic nerves; it displaces noradrenalinum from intraneuronal storage granules. This action does not inhibit the release of granule contents; it occurs through some unknown, mechanism. Much of the noradrenalinum released from the adrenergic nerve terminals is destroyed by the COMT and the MAO. Some noradrenalinum will still leak from the cell.

Pharmacokinetics: With oral administration, absorption varies and the onset of action is slow. The drug is rapidly cleared by the kidney.

Pharmacologic effects: A large intravenous dose causes a transient increase in blood pressure. This is followed by a fall in systemic and pulmonary arterial

pressures that is much more intense in the erect than in the supine individual. In high doses it has myorelaxant effect.

Therapeutic uses: The major therapeutic indication is a potent, long-acting antihypertensive agent.

Adverse effects include postural hypotension, syncope, especially with strenuous exercise, diarrhea, and edema. Guanethidine is contraindicated in patients taking the MAO inhibitors. The antihypertensive effects of guanethidine may be reversed by tricyclic antidepressants or indirect-acting sympathomimetic amines, such as ephedrinum hydrochloridum.

Ornidun (Bretylum)

Pharmacologic effects: Ornidun is taken up by adrenergic nerve terminals, it produces a block in the release of noradrenalinum. It is not used in Ukraine.

Methyldopha (dopegyt) is an agonist of α_2 presynaptic adrenergic receptors which cause depressive stimulus to vasomotor center. It is also converted into α -methylnoradrenaline, it is a weaker vasoconstrictive agent than noradrenalinum and decreases level of rennin. Methyldopha has antihypertensive affect due to the fall of common vessel peripheral resistance and use in arterial hypertension.

N ^o	Drug	Drug forms
1.	Adrenalini hydrochloridum	Amp. 0,1% 1ml
2.	Noradrenalini hydrotartras	Amp. 0,2% 1ml
3.	Mesatonum	Pulv.; Amp. 1% 1ml Guttae 1-2%
4.	Galazolinum (Xylometazolinum)	Flac. 0,1%, 0,05% - 10ml
5.	Salbutamololum	Tab. 0,002; Flac. 0,4% - 10ml
6.	Fenoterolum	Flac. 15ml
7.		
8.	Ephedrini hydrochloridum	Pulv.; Tab. 0,025; Amp. 5% - 1ml;

		2-3% - 10ml
9.	Prazosinum	Tab. 0,001, 0,002, 0,0005
10.	Pyroxanum	Tab. 0,015 Amp. 1% 1ml
11.	Doxazosinum	Tab. 0,002, 0,004
12.	Anaprilinum	Tab. 0,01-0,04; Amp. 0,1% - 1ml
13.	Metoprololum	Tab. 0,05, 0,1 Amp. 1% - 5ml
14.	Atenololum	Tab. 0,025; 0,05; 0,1
15.	Reserpinum	Pulv.; Tab. 0,0001, 0,00025
16.	Methyldopha	Tab. 0,25

PARASYMPATHETIC (CHOLINERGIC) AGONISTS

These drugs are divided into:

1. M-N-cholinomimetic agents (acetylcholini chloridum, carbocholinum, bethanecholum).
2. M-cholinomimetic agents (pilocarpini hydrochloridum, aceclidinum)
3. Anticholinesterase agents (proserinum, pyridostigmini bromidum, galanthamini hydrobromidum, physostigmini salicylas, phosphacolum, arminum).
4. N-cholinomimetic agents (cytitonum, lobelini hydrochloridum).

Acetylcholini chloridum is a quaternary ammonium ester which is rapidly hydrolyzed by acetylcholinesterase and plasma cholinesterase.

Pharmacologic and Cardiovascular effects: a negative inotropic effect, a negative chronotropic effect, vasodilatation, its actions on the heart are the same as the effects of vagal stimulation, big intravenous doses cause an increase in blood pressure, owing to the release of catecholamines from the adrenal medulla and activation of sympathetic ganglia.

Effects on other systems: acetylcholine increases gastrointestinal motility and secretory activity; it contracts smooth muscle in the uterus, ureters, bladder, and bronchioles, and constrictor muscles of the iris (may decrease intraocular pressure,

provokes myosis); it stimulates the salivary, sweat, and lachrymal glands, it does not influence the CNS.

Therapeutic uses: Acetylcholini chloridum is not now used in clinical practice.

Carbacholinum (carbachol). Carbacholinum has a carbamic acid-ester link, which is not readily susceptible to hydrolysis by cholinesterases. Carbacholinum has all the pharmacologic properties of acetylcholinum. It exerts both nicotinic and muscarinic effects and increases release of acetylcholinum from vesicles. Carbacholinum is used ophthalmically for decrease intra-optical pressure.

Bethanecholum. Chemically bethanechol has the structural features of both methacholine and carbacholinum. It is resistant to hydrolysis by cholinesterases and is mainly muscarinic in action. It is not used in Ukraine.

Pilocarpini hydrochloridum. Pilocarpini hydrochloridum is a tertiary amine alkaloid. Its actions are similar to those of acetylcholinum. When applied locally to the eye, it causes miosis and an eventual fall in intraocular pressure. Its major therapeutic indication is in the treatment of glaucoma and seldom in xerostoma.

Aceclidinum stimulates more contraction of intestines, it uses more often in the case of atonia of intestine and urine bladder.

Cytitonum is a drug of alkaloid cytizine. Cytitonum stimulates N-cholinoreceptors of sinocarotid zone, sensitizes vasomotor center, increases blood pressure, stimulates breathing. It is used in asphyxia.

Lobelini hydrochloridum is also alkaloid. Its pharmacodynamics is similar to cytitonum, but its transitory decreases blood pressure thanks to stimulation of centre pneumogastric nerve. It is also used in asphyxia.

ANTICHOLINESTERASE AGENTS

All these drugs are divided into medicaments of **reversible** and **irreversible** action (phosphororganic drugs). The drugs of reversible action are divided into tertiary amines which penetrate through haemato-encephalic barrier and quaternary amines which do not penetrate.

Physostigmini salicylas

Mechanism of action: This alkaloid forms a reversible complex at the site of acetylcholinesterase where acetylcholine is broken down.

Pharmacokinetics: Physostigmini salicylas is well absorbed from the gastrointestinal tract, subcutaneous tissues, and mucous membranes. Its metabolism is at the ester linkage by hydrolytic cleavage.

Pharmacologic effects: The pharmacologic properties of physostigmini salicylas identical to those of acetylcholine, have tertiary nitrogen, penetrate across hematoencephalic barrier and have stimulate action on the CNS. It produces miosis and decreases intraocular pressure and, thus, can antagonize the mydriasis induced by atropini sulfas. When given in big doses, it causes fasciculation, then paralysis, of skeletal muscle because of the accumulation of acetylcholine at the neuromuscular junction that results when acetylcholine is not broken down.

Therapeutic uses: It is used for treatment of atropini sulfas, other cholinoblockers and tricyclic antidepressant intoxication. Treatment of glaucoma, especially simple and secondary glaucoma. Treatment of early stages of Alzheimer's disease, since degeneration of cortical cholinergic axons has been seen at autopsy in some patients with this disorder.

Galanthamini hydrobromidum has also tertiary nitrogen and is used as physostigmini salicylas. It acts slower but longer, it has irritative effect that is why it is not used in glaucoma.

Proserinum (Neostigmine)

Pharmacokinetics: Proserinum is a synthetic reversible anticholinesterase that contains quaternary nitrogen. Proserinum is not well absorbed orally. It does not penetrate the blood-brain barrier, which minimizes the toxicity due to inhibition of acetyl cholinesterase that is in the brain. It is destroyed by plasma esterases and is excreted in the urine.

Pharmacologic effects: The pharmacologic properties of proserinum similar to those of acetylcholine. It also has a direct action on nicotinic receptors, in addition

to blocking acetyl cholinesterase. It reverses the neuromuscular blockade produced by curare and its derivatives; the mechanism of action involves the release of increased amounts of acetylcholine from nerve endings, cholinesterase inhibition, and a direct action on skeletal muscle cholinergic receptors.

Therapeutic uses: Proserinum is used to reverse the effects of competitive neuromuscular blocking agents. It is used in the management of paralytic ileus and atony of the urinary bladder. It is also used in the symptomatic treatment of myasthenia gravis.

Other anticholinesterases that have quaternary nitrogen. Pyridostigmini bromidum and distigmini bromidum are used in the symptomatic treatment of myasthenia gravis, atonia of intestines, and urine bladder.

Organophosphate cholinesterase inhibitors - phosphacolum, arminum are organophosphate compounds, which form a covalent bond between its phosphorus atom and the esteratic site of cholinesterase. The enzyme-inhibitor complex thus formed is irreversible. Its use is limited to the treatment of certain types of glaucoma.

Arminum is a long-acting organophosphate cholinesterase inhibitor with pharmacologic properties similar to those of phosphacolum. Spontaneous regeneration of the phosphorylated enzyme can occur. Its major use is in the treatment of glaucoma.

Adverse effects: Miosis, increased bronchial secretions, profuse sweating, and increased lacrimation, anorexia, vomiting, and involuntary diarrhea, bradycardia, weakness of all skeletal muscles, rout especially those of respiration, after twitching and fasciculations, anxiety, confusion, and convulsions, followed by vasomotor depression.

Reversal of cholinesterase inhibition: Reactivators of cholinesterase - dipyroximum, alloximum, isonitrosinum, reverse the effects of the organophosphate anticholinesterase agents according to interaction with them, or only with a phosphorus group.

They combine **with and splits** off the phosphorus from the esteratic site on cholinesterase in such a way that the enzyme is restored, they may defend enzyme, it has M-cholinoblocking properties. With reactivation of the enzyme, the effects of acetylcholine begin to disappear. Treatment must be within hours, because the phosphorylated enzyme slowly changes to a form that cannot be reversed.

№	Drug	Drug forms
1.	Carbacholinum	Flac. 0,5%, 1% - 5, 10ml
2.	Pilocarpini hydrochloridum	Flac. 1%, 2% - 5, 10ml; Ung. 1%, 2%
3.	Proserinum	Pulv.; Tab. 0,015 Amp. 0.05% 1ml
4.	Galanthamini hydrobromidum	Amp. 0,1%, 0,25%, 0,5%, 1% - 1ml
5.	Pyridostigmini bromidum	Tab. 0,01 Dragee 0,06 Amp. 0,1% - 1ml
6.	Phosphacolum	Flac. 0,013%, 0,02% - 10ml
7.	Dipiroximum	Pulv.; Amp. 15% - 1ml
8.	Alloximum	Amp. 0,075

PARASYMPATHETIC ANTAGONIST (Cholinoblocking agents)

1. M-cholinoblocking agents (atropini sulfas, platyphyllini hydrotartras, scopolamini hydrobromidum, extractum Belladonnae sicum, methacinum, ipratropii bromidum, pirenzepinum).

2. N-cholinoblocking agents:

a. Ganglioblocking agents – benzohexonium, pentaminum, hygronium, pirilenum;

b. Myorelaxants – Tubocurarini chloridum, pipecuronii bromidum, dithylinum etc.

3. M-N-cholinoblocking agents (central blocking agents) – amizylum, cyclodolum, tropacinum.

M-cholinoblocking agents

Atropini sulfas is an alkaloid derived from the plant *Atropa belladonna* (deadly nightshade). An active component is a racemic mixture *dl*-hyoscyamine, an ester compound of tropic acid and an organic base tropine.

Mechanism of action: Atropini sulfas competes reversibly with acetylcholine at muscarinic receptors. At very high concentrations, it blocks acetylcholine at ganglionic synapses and motor nerve endings. Atropini sulfas antagonizes the action of acetylcholine in the CNS.

Pharmacokinetics: Atropini sulfas is rapidly but poorly absorbed when given orally, it is biotransformed in the liver. It disappears rapidly from the blood and is excreted in the urine.

Pharmacologic effects and Effects on the heart: tachycardia then follows with increased cardiac output and shortening of the P-R interval. **Effects on blood pressure:** oral or intramuscular doses practically have no effect on blood pressure while with intravenous injection, total peripheral resistance increases. Due to the rise in heart rate and cardiac output, arterial pressure may increase and atropini sulfas has a direct vasodilating effect on small blood vessels.

Effects on the CNS: big doses can produce excitation (hallucinations etc.) and, ultimately, coma, but therapeutic doses exert little exciting effect; atropini sulfas possesses antitremor activity via a central antimuscarinic mechanism.

Effects on involuntary muscles: atropini sulfas decreases the amplitude and frequency of peristaltic contractions and reduces the tone of the stomach, small intestine and colon; it also relaxes the smooth muscle of the biliary tract; bladder and ureter to PGE₂ are decreased, while vesical sphincter tone is increased.

Effects on the eye: atropini sulfas blocks the acetylcholine response of the ciliary muscle of the lens and of the circular smooth muscles of the iris, producing cycloplegia and mydriasis; it may increase intraocular pressure; it may cause local anaesthesia in eye drops.

Effects on secretions: sweat gland secretions are greatly reduced; bronchial and salivary secretions are decreased; there is a reduction in gastric secretion and reduction in total acid content.

Effects on the bronchi: atropini sulfas produces slight bronchodilatation.

Therapeutic uses: Ophthalmic administration is used for producing cycloplegia after trauma and mydriasis for diagnostics. Its ability to reduce secretions in the upper and lower respiratory tract makes it useful as a preanesthetic agent. It is used to treat sinus node bradycardia or a high-grade A-V block. It is effective for prophylaxis of motion sickness. Combined with an opioid, it is used for the treatment of renal and biliary colic. It may be used in large doses for the treatment of poisoning by anticholinesterase and cholinomimetic agents and for the rapid type of mushroom poisoning, because it antagonizes the actions of acetylcholine.

Adverse effects: Rapid pulse, dilated pupils, resulting in photophobia, dry mouth, flushed skin, a rise in body temperature, especially in children, restlessness, confusion, and disorientation.

The **antidote** in atropini sulfas poisoning is galanthamini salicylas, physostigmini salicylas or other anticholinesterase drugs.

Scopolamini hydrochloridum (hyoscine), like atropini sulfas, is an alkaloid and is an ester of tropic acid but with the organic base scopine.

Pharmacologic effects: Like atropini sulfas, scopolamine hydrochloridum has antimuscarinic actions. It is more potent than atropini sulfas in producing mydriasis and cycloplegia, in decreasing bronchial, salivary, and sweat gland secretions, and in its sedative effect. It is less potent than atropini sulfas in its effects on the heart, bronchial muscles, and intestines. Atropini sulfas has a longer duration of action and in therapeutic doses it does not depress the CNS.

Therapeutic uses and adverse effects are generally similar to those of atropini sulfas. Scopolamini hydrochloridum is excellent for motion sickness, parkinsonism, airsickness and seasickness. It is a component of a drug "Aeronum" for airsickness and seasickness.

Platphyllini hydrotartras is an alkaloid, it has more expressive than atropine sulfate influence upon the smooth muscle, it decreases pressure. It is used in spasms of smooth muscles and hypertonic crises.

Dry extract of deadly nightshade **Extractum Belladonnae siccum** is a spasmolytic drug.

Ipratropii bromidum (Atrovent) does not influence the CNS, it widens bronchial muscles.

Pirenzepinum (Gastrocepinum) decreases secretion of acidum hydrochloricum, gastrinum. It influences M₁-cholinoreceptors.

Methacinum is a synthetic antimuscarinic agent. It does not influence the CNS. It is useful in the treatment of bladder and intestine spasm. At normal therapeutic doses, it decreases spasm in most smooth muscles without producing atropine-like effects on the heart, eye, or salivary and sweat glands. It is thought to act by direct relaxation of muscle rather than by competitive antagonism of acetylcholine at muscarinic receptors.

Homatropini hydrochloridum is used in ophthalmology. It is a rapidly acting muscarinic blocking agent used to produce cycloplegia and mydriasis for ophthalmic refractions.

NEUROMUSCULAR BLOCKING AGENTS (MYORELAXANTS)

These agents, which act by blocking transmission at the neuromuscular junction, can be divided into two classes on the basis of their mechanism of action: **depolarizing agents** and **competitive, or stabilizing blocking agents**. Dioxonium is the drug of mixtural action.

Mechanism of action.

1. Depolarizing agents (dithylinum, succinylcholine)

a. Like acetylcholine, depolarizing agents react with receptors at the muscle end-plate leading to depolarization of the excitable membrane. This **phase I block** is seen clinically as fasciculation.

b. With prolonged exposure a reduction in receptor sensitivity occurs, leading to a **phase II**, or **desensitization, block** manifested by flaccid paralysis. This phase II block is not competitive in nature.

2. Competitive blocking agents (tubocurarine chloridum, pancuronium bromidum, atracurium besilate, vecuronium, metocurinium, pipercuronium bromidum, rocuronium bromidum):

a. Competitive blocking agents combine with acetylcholine receptors at the muscle end-plate but do not activate them;

b. By decreasing the number of available acetylcholine receptors, these agents reduce the height of the end-plate potential; thus, the threshold for excitation is not reached;

c. They may cause histamine release and blood pressure fall, but steroid derivatives (pipercuronium bromidum, pancuronium bromidum, vecuronium, rocuronium bromidum) practically do not provoke such effect.

Pharmacokinetics: After injection of a neuromuscular blocking agent it is found in high concentration in venous blood flowing to the heart and ultimately in the extracellular space around the muscle end-plate. Succinylcholine has a rapid onset of action, which facilitates rapid endotracheal intubation. Atracurium besilate has a longer onset of action than Succinylcholine and spontaneous recovery occurs after 30-60 minutes.

Metabolism: Metabolism of tubocurarine chloridum is negligible. Pancuronium bromidum, rocuronium bromidum is deacetylated and its metabolites show some activity. Succinylcholine is rapidly metabolized to succinylmonocholine and choline, which accounts for its brief duration of action. Atracurium besilate is inactivated in the plasma by enzymatic ester hydrolysis.

Therapeutic uses: Neuromuscular blocking agents are used as surgical adjuvants to anesthesia for promoting skeletal muscle relaxation; for facilitating endotracheal intubation; with electroconvulsant shock therapy to prevent trauma; in

the diagnosis of myasthenia gravis (tubocurariini chloridum), although provocative tests of this sort are potentially hazardous procedures.

Pipercuronii bromidum: Pipecuronii bromidum does not have vagolytic activity nor does it cause histamine release.

Adverse effects: All neuromuscular blocking agents do not affect the sensorium, so that despite the paralysis, individuals remain conscious and are able to feel pain; prolonged apnea may occur.

Depolarizing agents: fasciculations can cause muscle pain; this occurs most frequently in young patients; fasciculations of the abdominal muscles can result in increased intragastric pressure. This is important in patients at risk of aspirating gastric contents. Contraction of extraocular muscles can lead to an increase in intraocular pressure. The muscle fasciculations and the increased intraocular and intragastric pressure may be diminished by a prior administration of a small dose of a competitive blocking agent. Succinylcholine may exert some action at other acetylcholine receptors, such as stimulation of autonomic ganglia and muscarinic receptors. The resulting effects, such as bradycardia and increased bronchial secretions, are seen more commonly with repeated intravenous administration in children. Cardiac arrest has occurred. In some genetically predisposed individuals the combination of succinylcholine and halothane results in a rapid and potentially fatal rise in temperature (malignant hyperthermia).

Tubocurariini chloridum. A dose-related fall in arterial pressure, the most common side effect, is the result of both ganglionic blockade and histamine release. Histamine release can also result in bronchospasm.

Metocurini chloridum causes histamine release less often than tubocurariini chloridum does. **Atracurii besilate** is a less potent histamine releaser than either tubocurariini chloridum or metocurini chloridum.

Vecuronium causes no histamine release; thus, the risk of histamine-induced hypotension or bronchoconstriction is reduced.

Pancuronii bromidum also causes an increase in the heart rate and in arterial pressure.

Pipercuronii bromidum can have a prolonged duration of action in patients with renal failure. **Rocuronii bromidum** has less influence on the cardio-vascular system.

Factors influencing the action of neuromuscular blocking agents: Serum cholinesterase is determined genetically. Normally transient effects of succinylcholine will be greatly prolonged in an individual with deficient serum cholinesterase. Because serum cholinesterase is synthesized in the liver, hepatic disease can double the duration of action of succinylcholine. Patients with myasthenia gravis are highly sensitive to competitive neuromuscular blocking agents, and phase II block occurs sooner than in normal individuals when depolarizing blockers are given. Patients with Eaton-Lambert syndrome (small cell or oat cell, carcinoma of the lung) have increased sensitivity to both competitive and depolarizing neuromuscular blockers. Depolarizing neuromuscular blockers increase serum potassium. This is exacerbated in conditions that are associated with hyperkalemia, such as burns. Aminoglycoside antibiotics and lincomycin exert a synergistic neuromuscular blockade when given with either competitive or depolarizing neuromuscular blocking agents. The mechanism is presynaptic. All inhalation anesthetics increase the effects of neuromuscular blocking agents.

Reversal of neuromuscular blockade

Competitive neuromuscular blockers can be antagonized by cholinesterase inhibitors, such as proserinum, pyridostigmini bromidum, galanthamini hydrobromidum. No antagonists currently exist for depolarizing blockers. Controlled ventilation is used until spontaneous recovery occurs. If an anticholinesterase is given, phase I block increases, but an anticholinesterase may reverse phase II block.

There are **myorelaxants of central action** (baclofenum, tizanidinum, tolperizonum, tetrazepamum) with different mechanism of action, which is used in the treatment of painful muscle spasm.

Ganglioblocking agents

Ganglioblocking agents are divided into tertiary amines - pirilenium and quaternary amines – benzohexonium, pentaminum, hygronium.

Blockers of ganglionic nicotinic receptors act like competitive pharmacologic antagonists, though there is evidence that they can also block the nicotinic channel pore. These drugs were the first successful agents for the treatment of hypertension. **Benzohexonium, pentaminum** are Ganglioblocking agents and were extensively used for this disease before. Unfortunately the adverse effects of ganglion blockade in hypertension are so severe (both sympathetic and parasympathetic divisions are blocked) that patients were unable to tolerate them for long periods. As a result of influence on sympathetic ganglions they widen arteries and veins, decrease arterial pressure, pre- and postloading on myocardium. As a result of influence on parasympathetic ganglions they have spasmolytic effects and decrease secretion. Recent interest has been focused on nicotinic receptors in the CNS and their relation to nicotine addiction and to Tourette's syndrome. Paradoxically, both nicotine (in the form of nicotine patches) and mecamylamine, a ganglion blocker that enters the CNS, have been shown to have some benefit in these applications. Because ganglion blockers interrupt sympathetic control of venous tone, they cause marked venous pooling. Postural hypotension is a major manifestation of this effect. Other toxicities of ganglion blocking drugs include dry mouth, blurred vision, constipation, and severe sexual dysfunction. They are used in hypertensive crises for **leading to hypotension (hygronium)** and edema of lungs.

M-N-cholinoblocking agents are different. Amizylum influences more M-cholinoreceptors and is a tranquilizer. Tropaminum influences more **H- and cyclodolum** on M- and N-cholinoreceptors. They are antiparckinsonic drugs.

	Drug	Drug forms
1.	Atropini sulfas	Pulv.; Tab. 0,0005; Amp. 0,1% - 1ml; Guttae 1%; Ung. 1%

2.	Extr. Belladonnae siccum	Pulv.
3.	Platyphyllini hydrotartras	Pulv.; Tab. 0,005; Amp. 0,2% 1ml
4.	Scopolamini hydrobromidum	Pulv.; Amp. 0,05% 1ml
5.	Methacinum	Tab. 0,002; Amp. 0,1% 1ml
6.	Ipratropii bromidum	Flac. 15ml
7.	Pirenzepinum	Tab.0,025, 0,05; Amp.0,5% 2ml
8.	Benzohexonium	Tab. 0,1; Amp. 2,5% 1ml
9.	Pentaminum	Amp. 5% 1ml
10.	Tubocurarini chloridum	Amp. 1% 1,5ml
11.	Pipecuronii bromidum	Amp. 0,004
12.	Dithylinum	Pulv.; Amp. 2% - 5ml
13.	Cyclodolum	Tab. 0,001, 0,002, 0,005

Adrenergic drugs **are divided into:**

1. Adrenomimetic drugs;
2. Antiadrenergic drugs;

ADRENOMIMETIC AGENTS.

These are drugs that mimic the actions of the sympathetic nervous system. Adrenomimetic drugs are divided into medicaments of direct and indirect action. Adrenomimetic drugs of direct action sensitize adrenoceptors similar to mediator directly. They include:

- 1) α, β adrenomimetic drugs – adrenalini hydrochloridum, noradrenalini hydrotartas.
- 2) α adrenomimetic drugs:
 - α_1 (mainly) - mesatonum
 - α_2 (mainly) – xylomethazolinum, naphthyzinum.

3) β - adrenomimetic:

$\beta_1\beta_2$ – isadrinum, orciprenalini sulfas

β_1 - dobutaminum

β_2 – salbutamolum, fenoterolum.

Adrenomimetic drugs of indirect action (sympathomimetic) may release mediators from labil vesicles, brake the reuptake, inhibit MAO and increase sensitivity of adrenoceptors to mediators.

Ephedrini hydrochloridum belongs to adrenomimetic drugs of indirect action.

Pharmacokinetics: The drugs similar to endogenous adrenoceptor agonists (adrenalini hydrochloridum, noradrenalini hydrotartras, and dopaminum) rapidly metabolized by COMT and MAO. As a result, these adrenoceptor agonists are inactive when given by the oral route. These agonists have a short duration of action. When given parenterally, they do not enter the CNS in significant amounts. Isadrinum, a synthetic catecholamine, is similar to the endogenous transmitters but is not readily taken up into the nerve ending. Mesatonum is resistant to MAO and COMT. These agents are orally active; they enter the CNS, and their effects last much longer than do those of catecholamines.

Adrenalini hydrochloridum (epinephrine)

Pharmacokinetics: Absorption is poor with oral administration because the drugs are rapidly conjugated and oxidized. Absorption is slow with subcutaneous administration (duration of action 30 minutes) because the drugs cause local vasoconstriction. It may be administered intramuscularly also. The drug can be given intravenously (duration of action 5 minutes), but this route must be used with caution so that the heart does not fibrillate. The drug may be administered into heart with caution on the background of atropine sulfate. The liver is important in the degradation of adrenalinum. The majority of the dose is metabolized by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), and the metabolites and some of nonmetabolized adrenalinum are excreted in the urine.

Pharmacologic effects: Adrenalini hydrochloridum interacts strongly with both

β and α receptors. Its effects on some body systems depend on the concentration of adrenalini hydrochloridum as well as the type of receptor. At low concentrations, β effects predominate, and at high concentrations, α effects predominate.

Mechanisms of action: Alpha₁ receptor effects: Alpha₁ receptor effects are mediated primarily by the coupling protein G_q, which leads to activation of the phosphoinositide cascade and the release of inositol-1, 4, 5-trisphosphate (IP₃) and diacylglycerol (DAG) from membrane lipids. Calcium is subsequently released from stores in smooth muscle cells, and enzymes are activated. Direct gating of calcium channels may also play a role in increasing intracellular calcium concentration. Alpha₂ receptor effects: Alpha₂ receptor activation results in inhibition of adenylylcyclase via the coupling protein G_i. Beta receptor effects: Beta receptors (β_1 , β_2 , and β_3) stimulate adenylylcyclase via the coupling protein G_s, which leads to an increase in cAMP concentration in the cell. Effect on CNS is weak, such as headache, nausea, fibrillations of skeletal muscles.

Effects on blood pressure: A large dose of adrenalini hydrochloridum, administered intravenously, causes an increase in blood pressure, the systolic pressure increasing more than the diastolic. Subsequently, the mean pressure falls below normal before returning to the control value. The first rise in pressure is due to ventricular contraction through activation of β_1 receptors, then there is the decrease of pressure by stimulation centre of pneumogastric nerve. The second rise of pressure is connected with vasoconstriction through activation of α_1 receptors. An initial increase in heart rate, which, at the height of the vasopressor response, will be slowed by a compensatory vagal discharge. Then the pressure may decrease because of stimulation β_2 -adrenoreceptors. Low doses also cause a fall in blood pressure because the β_2 (vasodilator) receptors are more sensitive to adrenalini hydrochloridum than are the α (vasoconstrictor) receptors.

Vascular effects: Adrenalini hydrochloridum exerts its action on small arterioles and precapillary sphincters. It may delay the coronary, brain and skeletal muscles vessels and constrict the cutaneous and peritoneal vessels. Its vascular

effects include: decreased cutaneous blood flow; increased blood flow to skeletal muscle at low concentrations and decreased flow at higher concentrations; increased hepatic blood flow with increased splanchnic vascular resistance; increased renal vascular resistance, producing decreased renal blood flow; increased arterial and venous pulmonary pressure; increased coronary blood flow, caused indirectly by an increase in the work of the heart, and mediated by local effectors.

Effects on the heart produced by adrenalini hydrochloridum include: a direct effect on β_1 receptors, producing a slight initial increase in heart rate, which is slowed by a compensatory vagal discharge; increased stroke volume; increased cardiac output. These effects are connected with adenylyl cyclase activation, increase of cAMP level, glycolysis, glycogenolysis, lipolysis activation; a propensity toward arrhythmias.

Effects on smooth muscle depend on the predominant type of adrenergic receptor in the muscle. Adrenalini hydrochloridum relaxes gastrointestinal smooth muscle (α_2 and β -receptor stimulation), while it usually increases sphincter contraction (α stimulation). Uterine contractions may be inhibited (β) or stimulated (α), depending on menstrual phase or state of gestation. In the bladder, the detrusor muscle relaxes (β), while the trigone and sphincter contract (α). Bronchiolar smooth muscle relaxes (β_2).

Metabolic effects of adrenalini hydrochloridum also depend on the type of adrenergic receptor. These effects include: an increase in glucose and lactate production via liver and muscle glycogenolysis (β_2); inhibition of insulin secretion (α); an increase in free fatty acids, mediated by cyclic adenosine 3', 5'-monophosphate [cyclic AMP] (β_1); an increase in oxygen consumption; antiallergic effects is connected with decrease of histamine level

Effects on eyes: adrenalini hydrochloridum produces mydriases, reduces intraocular pressure in patients with open-angle glaucoma.

Pharmacologic effects of noradrenalini hydrotartras (norepinephrine). An intravenous infusion raises both systolic and diastolic pressure by constriction of

vascular smooth muscle (α receptors) more than adrenalini hydrochloridum. The increased peripheral vascular resistance produces a compensatory vagal reflex that slows the heart rate. Cardiac output may actually decrease although coronary blood flow is increased. The drug has less effects on metabolism, intestines, doesn't influence on bronchus.

Therapeutic uses: Adrenalini hydrochloridum is used: to treat bronchospasm; for relief of hypersensitivity reactions; it is the primary treatment for anaphylactic shock; to prolong the duration of infiltrative anesthesia; to restore cardiac activity in cardiac arrest; to facilitate aqueous drainage in chronic open-angle glaucoma. Noradrenalini hydrochloridum is used for treating hypotension during anesthesia when tissue perfusion is good, other status with hypotension and shock.

Adverse effects: Both adrenalini hydrochloridum and noradrenalini hydrochloridum can cause: anxiety, headache, cerebral hemorrhage from the vasopressor effects, cardiac arrhythmias, especially in the presence of digitalis and certain anesthetic agents, pulmonary edema from pulmonary hypertension, hypertension.

Isadrinum (isoproterenol)

Pharmacokinetics. Absorption of orally administered isadrinum is unreliable, it is given sublingually. It is readily absorbed when given parenterally or as an inhaled aerosol. It is principally metabolized by COMT; MAO plays a much smaller role than in adrenalini hydrochloridum or noradrenalini hydrochloridum metabolism.

Pharmacologic effects. Isadrinum has an *N*-alkyl substitution, which makes it act almost entirely on β receptors and have very little effect on α receptors. Intravenous infusion produces a reduction of peripheral vascular resistance in skeletal muscles and in renal and mesenteric vascular beds. Diastolic blood pressure falls, but owing to increased venous return and positive inotropic and chronotropic effects, cardiac output is increased. Systolic blood pressure may increase, but mean pressure decreases. Renal blood flow decreases in normotensive individuals, but it increases in patients with nonhemorrhagic shock. Relaxation of both bronchial and gastrointestinal smooth muscle occurs. A release of free fatty acids occurs; hyperglycemia is less than with adrenalini hydrochloridum. Pancreatic islet cells are

activated, stimulating insulin secretion.

Therapeutic uses: Isadrinum is used as a bronchodilator and more often as a cardiac stimulant.

Adverse effects: These are similar to the adverse effects of adrenalini hydrochloridum. Overdosage by inhalation can induce fatal ventricular arrhythmias. Tolerance to the desired effects occurs with overuse in the asthmatic.

Orciprenalini sulfas (Alupent) influences more expressively on β_2 -adrenoreceptors. The drug decrease arterial pressure and produces tachycardia less than isadrinum. It use as bronchodilatator.

Dopaminum. Dopaminum is an intermediate in the synthesis of noradrenalinum.

Pharmacokinetics: Dopaminum resembles adrenalini hydrochloridum and noradrenalini hydrotartras in its pharmacokinetics.

Central dopamine receptors (D_1 , D_2 , D_3)

a. The central D_1 receptor site is excitatory and directly activates the adenylate cyclase system.

b. The D_2 receptor site is inhibitory in some brain tissues and uses cAMP as its intracellular messenger. Pituitary-related side effects of neuroleptics are thought to be mediated through D_2 receptors in the pituitary.

c. The D_3 receptor is localized in the limbic system and is not found in the pituitary. It is principally associated with emotional and cognitive behavior.

Pharmacologic effects:

Dopaminum receptor effects: Dopaminum D_1 receptors activate adenylyl cyclase in neurons and vascular smooth muscle. Dopaminum D_2 receptors are more important in the brain but probably also play a significant role as presynaptic receptors on peripheral nerves. Dopaminum is an important neurotransmitter in the CNS. It is a direct agonist, acting on β_1 receptors and also releases noradrenalinum from nerve terminals. The result is a positive inotropic effect on the myocardium. Low or intermediate doses of dopamine reduce arterial resistance in the mesentery and kidney; this raises the glomerular filtration rate. The effect is mediated by a

receptor for dopaminum. Dopaminum increases systole pressure but has little effect on diastolic pressure. At higher doses, it acts on α receptors and causes vasoconstriction with a consequent reduction in renal function.

Therapeutic uses: Dopaminum is used in the treatment of carcinogenic and septic shock and in chronic refractory congestive heart failure.

Adverse effects: Overdosage results in excessive sympathomimetic activity. Anginal pain, arrhythmias, nausea, and hypertension can occur, but these effects are short-lived because of dopamine's rapid metabolism.

Dobutaminum

Pharmacokinetics: Dobutaminum is not absorbed when given orally. It has a half-life of 2 minutes when given by intravenous injection.

Pharmacologic effects: Though dobutaminum resembles dopaminum chemically, it is a direct β_1 -receptor agonist. It has a greater inotropic than chronotropic effect. Dobutaminum does not act on dopaminergic receptors.

Therapeutic uses: Dobutaminum is used to improve myocardial function in congestive heart failure. Oxygen demands are less than with other sympathetic agonists because dobutaminum causes minimal changes in heart rate and systolic pressure.

Adverse effects: Dobutaminum increases atrioventricular conduction and must, therefore, be used with caution in atrial fibrillation. Other adverse effects are similar to those of other catecholamines.

Mesatonum (phenylephrine)

Pharmacologic effects: Mesatonum has one hydroxyl group in the aromatic ring, practically is not destroyed administered orally. Mesatonum is a direct-acting synthetic sympathomimetic agent. Its effects are similar to those of noradrenalinum mainly on α_1 -adrenoreceptors, but it is less potent and has a longer duration of action, it decrease intra-ocular pressure also in oper-angular glaucoma. Vasoconstriction, increased atrial pressure, and reflex bradycardia occur with parenteral administration.

Therapeutic uses: Phenylephrine is used: as a nasal decongestant, as a

presser agent, to provide local vasoconstriction as an adjunct for use with local anesthetics, in ophthalmology as mydriatic agent.

Adverse effects: Large doses cause cardiac irregularities. Ophthalmic solutions, like intranasal solutions, can be systemically absorbed. Their use in patients taking β blockers increases the risk of cardiac irregularities, myocardial infarction, and intracranial hemorrhage. Rebound nasal congestion can occur with chronic use as a nasal decongestant.

Xylomethazolinum, naphthyzinum influence α_2 adrenoreceptors mainly and are used in the case of rhinitis.

Ephedrini hydrochloridum

Pharmacokinetics: Ephedrini hydrochloridum is absorbed when taken orally. It is resistant to COMT and MAO, so that its action is prolonged.

Pharmacologic effects: Ephedrini hydrochloridum is a sympathomimetic agent; that is, it has indirect action. Its primary action is indirect: It causes the release of noradrenalinum from storage in nerve terminals, apparently by competing with noradrenalinum for transport into the granules. It also increases sensitivity adrenergic receptors. When administered intravenously its action is similar to that of adrenalini hydrochloridum. Its presser response occurs more slowly and lasts 10 times longer. Its potency is 1/250 that of adrenalini hydrochloridum in producing an equivalent presser response. Ephedrini hydrochloridum increases arterial pressure by causing peripheral vasoconstriction and cardiac stimulation. Its effects on the bronchi and other smooth muscle are qualitatively similar to those of adrenalini hydrochloridum. It causes CNS stimulation, which can result in effects such as insomnia, nervousness, nausea, and agitation. Tachyphylaxis occurs with repeated administration.

Therapeutic uses: Ephedrini hydrochloridum is used very seldom: in the treatment of bronchial asthma; as a presser agent in spinal anesthesia for collapse prophylaxis.

Adverse effects: These are similar to the adverse effects seen with adrenalini hydrochloridum. In addition, the CNS effects may occur. Ephedrini hydrochloridum must be used with caution in patients with cardiovascular disease or hyperthyroidism

because it is a powerful heart stimulator. Ephedrini hydrochloridum causes drug dependence.

Phenaminum (Amphetamine)

Pharmacologic effects. Amphetamine acts indirectly by releasing noradrenalinum. Amphetamine is also a CNS stimulant. The dextrorotatory (*d*-) form is more active in the CNS than the levorotatory (*l*-) form. Amphetamine depresses the appetite, decreasing food intake, by affecting the feeding centre in the lateral hypothalamus. It increases metabolism to a small extent. Amphetamine is not used because of psychic and physical dependence.

β_2 -Stimulating bronchodilators (salbutamol (ventolin), fenoterol (berotek), terbutalin (bricanil) and others)

Pharmacologic effects: The adrenergic agents that are primarily β_2 agonists have a relaxing effect on bronchial smooth muscle and show little effect on cardiac β_1 receptors. It has also tocolytic effects duration of its action 2-5 hours.

Therapeutic uses: These agents are used therapeutically for the treatment of bronchial asthma or bronchospasm where their lack of cardiac stimulation is a decided advantage. They are used chiefly as aerosol inhalants; oral and injectable forms are also available. Salmeterol (Serevent), Formoterol (Foradyl), Clenbuterol act 12 hours and use for protection bronchospasm.

Adverse effects of the β_2 agonists are similar to those seen with the sympathomimetic drugs listed above. Even though their effects are primarily bronchial, they should be used with caution in patients with cardiovascular disease or hyperthyroidism because they can still stimulate (though minimally) β_1 receptors of the heart.

ANTIADRENERGIC DRUGS.

They divided into **sympatholytics**, **antiadrenergic agents** and **antiadrenergic blocking agents**. Antiadrenergic blocking agents are classified into:

- a. α -adrenergic blocking agents;
- b. β -adrenergic blocking agents;

c. α - β -adrenergic blocking agents.

α -adrenergic blocking agents may be:

a. $\alpha_1\alpha_2$ -adrenergic blocking agents – phentolaminum, pyrroxanum, dehydrate ergot alkaloids.

b. α_1 -adrenergic blocking agents – prazosinum, doxazosinum, terazosinum.

α -adrenergic blocking agents (α blockers)

Phentolaminum and pyrroxanum act by a reversible α -adrenergic blockade.

Pharmacologic effects: These agents produce vasodilation α_1 -postsynaptic receptors and reflex cardiac stimulation α_2 -presynaptic receptors. They decrease peripheral resistance and increase venous capacity. Both stimulate salivary, lacrimal, pancreatic, and respiratory tract secretions. They cause a gastric secretion that resembles the effect of histamine. Pyrroxanum influences diencephalic part. Pyrroxanum is absorbed when given orally and is rapidly excreted by the kidneys; phentolaminum is excreted more slowly. Both can be given parenterally.

Therapeutic uses: Phentolaminum has been used to control acute hypertensive episodes due to pheochromocytoma. In the past, phentolaminum was used as a diagnostic test for pheochromocytoma, but it has been replaced by assays for urinary catecholamines. Pyrroxanum can be used in the treatment of hypertension in the case of hypothalamic (diencephalic) damages. Phentolaminum has been used in the treatment of Raynaud's phenomenon.

Adverse effects: Both drugs can cause cardiac stimulation, leading to arrhythmias and anginal pain, especially after parenteral administration; they must be used with caution in patients with coronary artery disease. Tolazoline can produce a paradoxical hypertension. Because they induce gastrointestinal stimulation, both drugs must be used with caution in patients with peptic ulcer disease.

Prazosinum is a selective blocker of postsynaptic α_1 receptors, producing vasodilation.

Pharmacologic effects: Prazosinum reduces vascular tone in both resistance and capacitance vessels. It also block phosphodiesterase' activity. Because

prazosin has no effect on α_2 receptors, neurotransmitter feedback inhibition is maintained, so that prazosin causes only a small degree of tachycardia. It decreases arterial pressure with little change in cardiac output, heart rate, and right atrial pressure. It may be tachycardia. Prazosin block α_{2A} receptors of uretra, urine bladder, prostate. Prazosin reduces symptoms of obstruction and urinary urgency. Prazosin is used in arterial hypertension and prostate hyperplasia.

Doxazosin (Cardura), Terazosin (Kornam) act 24 hours and have the same actions and use. Tamsulosin (Omnic) – α_1 -adrenoblocker is used in urology only.

Dehydrated ergot alkaloids (dihydroergotaminum, dihydroergotoxinum, dihydroergocristinum)

Mechanism of action: These agents are α -adrenergic blockers as well as being serotonin agonists.

Pharmacologic effects: Dehydrated ergot alkaloids have sedative, antiemetic effect; they widen arteries and narrow veins. They are used in the cases of vestibular disturbances in the air and sea diseases. They directly stimulate smooth muscle of brain vessels, acting on serotonin receptors are used in migraine.

β -Adrenergic blocking agents (β blockers) are divided into selective and nonselective drugs, the drugs with and without sympathomimetic activity.

Drug	β-Blocking Selectivity
Labetololum	Nonselective β - and selective α_1 -blocking activity
Carvedilolum	Nonselective β - and selective α_1 -blocking activity
Nadololum	Nonselective
Pindololum	Nonselective intrinsic sympathomimetic
Propranololum	Nonselective
Timololum	Nonselective
Acebutololum	β_1 -selective, intrinsic sympathomimetic
Esmololum	β_1 -selective, intrinsic sympathomimetic
Celiprololum	β_1 -selective, intrinsic sympathomimetic, β_2 -agonist
Talinololum	β_1 -selective, intrinsic sympathomimetic

Atenololum	β_1 -selective
Betaxololum	B ₁ -selective
Metoprololum	B ₁ -selective
Bisoprololum	B ₁ -selective
Nebivololum	β_1 -selective

Propranololum (anaprilinum) is a nonselective β antagonist: It competes for both β_1 and β_2 receptors.

Pharmacokinetics: Although propranolol is completely absorbed from the gastrointestinal tract, a large portion of the drug is extracted by the liver before it enters the systemic circulation. Wide variation in the hepatic metabolism of the drug among individuals causes significant differences in the plasma concentrations attained. Propranololum is approximately 90% bound to plasma proteins. The elimination half time is approximately 3 hours for a small dose, but it is prolonged with larger doses and is significantly prolonged in the presence of cirrhosis. A metabolic product, 4-hydroxypropranolol is active but has a short half-life.

Pharmacologic effects: Propranololum decreases the heart rate and cardiac output and prolongs systole, has membranostabilising action. It decreases total coronary blood flow and oxygen consumption. It reduces blood flow to most tissues except the brain.

The antihypertensive effect of propranololum is slow to develop. Propranololum inhibits the renal secretion of rennin. It depresses sodium (Na⁺) excretion because it alters renal hemodynamics, an effect that is secondary to the decrease in cardiac output. Propranololum increases airway resistance by β_2 blockade. Since most of the effects of catecholamines on carbohydrate and fat metabolism are mediated by β receptors, propranololum will interfere with these events. Propranololum has sedative effect. Propranololum increases the contractility of bronchial, intestinal, uterine smooth muscles. Propranololum decreases intraocular pressure in open-angle glaucoma.

Therapeutic uses: Treatment of hypertension, often in combination with a diuretic. Prophylaxis of angina pectoris. Prophylaxis of supraventricular and ventricular arrhythmias. Long-term prophylaxis in patients who have had a myocardial infarction and are at high risk for infarction or sudden death. Management of hypertrophic obstructive cardiomyopathies to reduce the force of myocardial contractions. Management of hyperthyroidism and anxiety states to decrease the heart rate. Prophylaxis of migraine headaches.

Adverse effects and precautions: Propranolol can induce heart failure, especially in patients with compromised myocardial function. Rapid withdrawal can lead to "super sensitivity" of β -adrenergic receptors, which can provoke anginal attacks, arrhythmias, or myocardial infarction. Because propranolol increases airway resistance, it must be used with caution in asthmatics. Because of its effects on carbohydrate metabolism, the hypoglycemic action of insulin may be augmented. Therefore, diabetics being treated with insulin and persons prone to hypoglycemia must use propranolol with caution. Rash, fever, and purpura are characteristic of an allergic response and require discontinuation of the drug. Prolonged use may cause fatigue, depression, nightmares, sexual dysfunction, and peripheral arterial insufficiency. Because of its effects on peripheral blood flow, propranolol is contraindicated in patients with Raynaud's phenomenon and other peripheral vessels disorders.

Timololum is a nonselective β -adrenergic antagonist that is 5-10 times more potent than propranolol. Timololum lowers intraocular pressure by reducing the production of aqueous humor; the mechanism is not clear. It does not change the size of the pupil, and vision is not affected. Timololum, in the form of eye drops, is, therefore, useful in the treatment of glaucoma.

Nadololum is a nonselective β -adrenergic blocking agent that is not metabolized and is excreted unchanged in the urine. Its effect and adverse reactions are similar to those of propranololum, but it influence longer. The introductions are the same as propranololum.

Adverse effects: Metoprololol produces fewer deleterious effects in asthmatic patients because of its selective β_1 -adrenergic antagonism, but its use in asthmatics still requires caution. Other adverse effects are similar to those of propranolol.

Atenololum is a selective β_1 -adrenergic antagonist, hydrophilic, which is administered two times a day and doesn't influence CNS.

Betaxololum is a selective β_1 -adrenergic antagonist, which is administered once a day. It is more lipophilic than atenololum. It is also available as a topical formulation for the treatment of glaucoma.

Bisoprololum is a selective β_1 -adrenoblocking agent with long duration of action. It may be used in arterial hypertension and congestive heart failure.

Nebivololum has own vasodilative properties by means of ability to influence the synthesis of NO.

Agents that inhibit the action of adrenergic nerves (sympatholytics)

Reserpinum

Mechanism of action: Reserpinum, a rauwolfia alkaloid, acts via catecholamine depletion. It inhibits the uptake of noradrenalinum into vesicles, and intraneuronal degradation of noradrenalinum by MAO then occurs. It impairs then restores and synthesis of catecholamines, their connection with ATP in vesicles. This action takes place both centrally and peripherally.

Pharmacologic effects: Blood pressure decreases, which usually triggers reflex tachycardia in normal people through sympathetic stimulation. However, because sympathetic stores are depleted, bradycardia may ensue in people taking reserpinum. Sedation and neuroleptic effect often result, owing to the depleted stores of catecholamines and serotonin (5-hydroxytryptamine, 5-HT) in the brain. Vagotonic effects on gastrointestinal tract.

Therapeutic uses: The major therapeutic use of reserpinum is in the treatment of hypertension.

Adverse effects: sedation, psychic depression that may result in suicide, abdominal cramps and diarrhea, gastrointestinal ulceration, possible increased incidence of breast carcinoma

Raunatinum is the sum of rauwolfia alkaloids, novogalenic drug, using for hypertension treatment.

Octadinum (Guanethidine)

Mechanism of action: Octadinum acts presynaptically and is peripheral sympatholytic agent. It impairs the response to sympathetic stimulation by inhibiting the release of neurotransmitters from peripheral adrenergic neurons. Octadinum is taken up by adrenergic nerves; it displaces noradrenalinum from intraneuronal storage granules. This action does not inhibit the release of granule contents; that occurs through another, unknown, mechanism. Much of the noradrenalinum released from the adrenergic nerve terminals is destroyed by COMT and MAO. Some noradrenalinum will still leak from the cell.

Pharmacokinetics: With oral administration, absorption varies and the onset of action is slow. The drug is rapidly cleared by the kidney.

Pharmacologic effects: A large intravenous dose causes a transient increase in blood pressure. This is followed by a fall in systemic and pulmonary arterial pressures that is much more intense in the erect than in the supine individual. In high doses it has myorelaxant effect.

Therapeutic uses: The major therapeutic indication is a potent, long-acting antihypertensive agent.

Adverse effects include: postural hypotension, syncope, especially with strenuous exercise, diarrhea, edema, guanethidine is contraindicated in patients taking MAO inhibitors. The antihypertensive effects of guanethidine may be reversed by tricyclic antidepressants or indirect-acting sympathomimetic amines, such as ephedrinum hydrochloridum.

Ornidun (Bretylum). Pharmacologic effects. Ornidun is taken up by adrenergic nerve terminals, it produces a block in the release of noradrenalinum. It is not used in Ukraine.

Methyldopa (dopegyt) is agonist of α_2 presynaptic adrenergic receptors that cause depressive stimulus to vasomotor center. It also is converted to α -methylnoradrenaline, it is a weaker vasoconstrictive agent than noradrenalinum and decreases level of rennin. Methyldopa has antihypertensive affect accordingly to fall of common vessel peripheral resistance and use in arterial hypertension.

№	Drug	Drug forms
17.	Adrenalini hydrochloridum	Amp. 0,1% 1ml
18.	Noradrenalini hydrotartras	Amp. 0,2% 1ml
19.	Mesatonum	Pulv.; Amp. 1% 1ml Guttae 1-2%
20.	Galazolinum (Xylometazolinum)	Flac. 0,1%, 0,05% - 10ml
21.	Salbutamololum	Tab. 0,002; Flac. 0,4% - 10ml
22.	Fenoterolum	Flac. 15ml
23.		
24.	Ephedrini hydrochloridum	Pulv.; Tab. 0,025; Amp. 5% - 1ml; 2-3% - 10ml
25.	Prazosinum	Tab. 0,001, 0,002, 0,0005
26.	Pyroxanum	Tab. 0,015 Amp. 1% 1ml
27.	Doxazosinum	Tab. 0,002, 0,004
28.	Anaprilinum	Tab. 0,01-0,04; Amp. 0,1% - 1ml

29.	Metoprololum	Tab. 0,05, 0,1 Amp. 1% - 5ml
30.	Atenololum	Tab. 0,025; 0,05; 0,1
31.	Reserpinum	Pulv.; Tab. 0,0001, 0,00025
32.	Methyldopha	Tab. 0,25

Approximately 5% of brain neurons have receptors for ACh. Most CNS responses to ACh are mediated by a large family of G protein coupled muscarinic M_1 receptors which lead to slow excitation when activated. Dopamine exerts slow inhibitory actions at synapses in specific neuronal systems commonly via G protein-coupled activation of potassium channels. Dopaminergic pathways include nigrostriatal, mesolimbic, and tuberoinfundibular tracts. Three other dopamine receptor subtypes have been identified (D_3 , D_4 , and D_5). Noradrenergic neuron cell bodies are mainly located in the brain stem and lateral tegmental area of the pons. Most serotonin (5-hydroxytryptamine; 5-HT) pathways originate from cell bodies in the raphe or midline regions of the pons and upper brain stem. These pathways innervate most regions of the CNS. Multiple 5-HT receptor subtypes have been identified and, with the exception of the 5-HT_{1A} subtype, all are metabotropic. 5-HT_{1A} receptors and GABA_B receptors share the same potassium channel. Serotonin is inhibitory at many CNS sites but can cause excitation of some neurons depending on the receptor subtype activated. Both excitatory and inhibitory actions can occur on the same neuron if appropriate receptors are present. Most neurons in the brain are excited by glutamic acid. Subtypes of glutamate receptors include the NMDA (*N*-methyl-D-aspartate) receptor. The NMDA receptors appear to play a role in synaptic plasticity related to learning and memory. Excessive activation of the NMDA receptors following neuronal injury may be responsible for cell death. Glutamate metabotropic receptor activation can result in G-protein-coupled activation of phospholipase C or inhibition of adenylylcyclase. The GABA is the primary neurotransmitter mediating the IPSPs in neurons in the brain; it is also important in

the spinal cord. The GABA_A receptor activation opens chloride ion channels. The GABA_B receptors (activated by baclofen) are coupled to G proteins that either open potassium channels or close calcium channels. Fast IPSPs are blocked by the GABA_A receptor antagonists, and slow IPSPs are blocked by the GABA_B receptor antagonists. Drugs which influence GABAergic systems include sedative-hypnotics and some anticonvulsants. Glycine receptors, which are more numerous in the cord than in the brain.

Many peptides have been identified in the CNS, and some meet most or all of the criteria for acceptance as neurotransmitters. The best-defined ones are the opioid peptides (beta-endorphin, met- and leu-enkephalin, and dynorphin), which are distributed at all levels of the neuraxis.

The ability of an agent to affect the CNS function is dependent on its ability to cross or mediate an effect across the **blood-brain barrier**.

GENERAL ANESTHETICS

General anesthetics act on the CNS or autonomic nervous system (ANS) to produce analgesia, amnesia, or hypnosis. Used alone or in combination with other agents (e.g. preanesthetic medication), an optimum depth of anesthesia may be obtained for a variety of surgical procedures. **Inhalation anesthetics**, notably ether and nitrogenium oxydulation, revolutionized surgery after 1846, when their anesthetic properties were accepted by the medical community. **Intravenous anesthetics** are mostly used for induction of anesthesia (e.g., thiopental) before administration of more potent anesthetic agents. However, they can be used for some procedures of longer duration.

Neuroleptanesthesia is induced by combining a powerful narcotic analgesic with a neuroleptic agent together with the inhalation of nitrous oxide and oxygen. **Dissociative anesthesia**, such as that caused by ketamine, produces rapid analgesia and amnesia while maintaining laryngeal reflexes. **Preanesthetic medication** may include sedatives, opioids, tranquilizers, and anticholinergic agents.

General anesthetics are the drugs which cause status of general anesthesia. They are divided into:

1. Drugs for inhalant narcoses: ether pro narlosi, fthorothamm, isofluranum, enfluratum, and sevafluranum;

2. Drugs for noninhalant narcoses: nitrogenum oxydulatum, and xenonum.

The first liquid was ether which is not practically used now.

Inhalation anesthetics

General anesthesia is a state characterized by unconsciousness, analgesia, amnesia, skeletal muscle relaxation, and loss of reflexes. Modern anesthetics act very rapidly and achieve deep anesthesia quickly. With older and more slowly acting anesthetics, a progressively greater depth of central depression associated with increasing dose or time of exposure is traditionally described as **stages of anesthesia**:

Analgesia: a patient has decreased awareness of pain, sometimes with amnesia. Consciousness may be impaired but is not lost. **Disinhibition:** a patient appears to be delirious and excited. Amnesia occurs, reflexes are enhanced, and respiration is typically irregular; retching and incontinence may occur. **Surgical anesthesia:** a patient is unconscious and has no pain reflexes; respiration is very regular, and blood pressure is maintained. **Medullary depression:** a patient experiences severe respiratory and cardiovascular depression which requires mechanical and pharmacologic support.

Mechanisms of Action: The mechanisms of action of general anesthetics are increasing the threshold for firing of the CNS neurons. The potency of most inhaled anesthetics is proportionate to their lipid solubility. Possible mechanisms of action include effects on ion channels (potassium, sodium, and calcium) by interactions with membrane lipids or proteins and effects on central neurotransmitter mechanisms. A potential "target" is the GABA_A receptor, which is directly coupled to a chloride ion channel.

Effects of Inhaled Anesthetics

The CNS effects: Inhaled anesthetics decrease brain metabolic rate. They reduce vascular resistance and thus increase a cerebral blood flow. This may lead to an increase in intracranial pressure. High concentrations of enflurane may

cause spike-and-wave activity and muscle twitching, but this effect is unique to this drug. Though nitrogenum oxydulatum has low anesthetic potency, it exerts marked analgesic and amnestic actions. **Cardiovascular effects:** Most inhaled anesthetics moderately decrease arterial blood pressure. Enfluranum and phthorothanum are myocardial depressants which decrease cardiac output, while isofluranum causes peripheral vasodilatation. Sevafluranum has minimal effects on cardiovascular system. Nitrogenum oxydulatum is less likely to lower blood pressure than are other inhaled anesthetics. A blood flow to the liver and kidney is decreased by most inhaled agents. Phthorothanum may sensitize the myocardium to the arrhythmogenic effects of catecholamines.

Respiratory effects: Rate of respiration may be increased by inhaled anesthetics, but tidal volume and minute ventilation are decreased leading to an increase in arterial CO and tension. Inhaled anesthetics decrease ventilatory response to hypoxia even at subanesthetic concentrations (e.g. during recovery). Nitrogenum oxydulatum oxide has the smallest effect on respiration. Postoperative hepatitis rarely occurred following phthorothanum anesthesia in patients experiencing hypovolemic shock or other severe stress. Fluoride released by metabolism of enfluranum may cause renal insufficiency after prolonged anesthesia. Prolonged exposure to nitrous oxide decreases methionine synthase activity and may lead to megaloblastic anemia. Susceptible patients may develop **malignant hyperthermia** when exposed to halogenated anesthetics. This rare condition of uncontrolled release of calcium by the sarcoplasmic reticulum of skeletal muscle leads to muscle spasm, hyperthermia, and autonomic lability.

Diethyl ether is a highly flammable and explosive anesthetic agent, which essentially has been replaced by halogenated anesthetics.

Pharmacologic and Respiratory effects: The increased sympathetic activity produced by diethyl ether results in bronchodilatation. The respiratory response to carbon dioxide, although reduced, is maintained spontaneously by reflex excitation at peripheral sites.

Cardiovascular effects: Although diethyl ether is a myocardial depressant,

cardiac output and arterial blood pressure are maintained because of sympathetic activation; Vagal blockade also occurs with diethyl ether administration resulting in tachycardia.

Renal effects: Diethyl ether is a strong stimulant of antidiuretic hormone.

Hepatic effects: Sympathetic activation results in increased hepatic glycogenolysis.

Muscular effects: Diethyl ether is a good skeletal muscle relaxant because it causes the CNS depression at synaptic pathways in the spinal cord. In addition, diethyl ether has a curare-like action allowing a lower dose of neuromuscular blockers. Several aminoglycoside antibiotics augment this effect.

Adverse effects: When used as a sole agent to induce anesthesia, diethyl ether causes increased salivary secretions, vomiting, and laryngospasm.

Phthorothanum. Pharmacologic and Respiratory effects: Respirations become rapid and shallow and there is a reduction in the minute volume. It causes a reduction in the ventilatory response to carbon dioxide. This effect appears to be due to depression of central chemoreceptors. Phthorothanum produces bronchiolar dilation.

Cardiovascular effects: Phthorothanum causes a dose-dependent decrease in arterial blood pressure. Cutaneous blood flow may increase as blood vessels dilate. Myocardial contractility is depressed with phthorothanum administration. Phthorothanum interferes the action of norepinephrine and, thus, antagonizes a sympathetic response to arterial hypotension. Phthorothanum anesthesia depresses cardiac sympathetic activity, which can result in a slow heart rate. Although arrhythmias are uncommon, phthorothanum can increase the automaticity of the heart. This condition is exacerbated by adrenergic agonists, cardiac disease, hypoxia, and electrolyte abnormalities. **The CNS effects:** As phthorothanum anesthesia deepens, fast, low-voltage electroencephalographic waves are replaced by slow, high-voltage waves. Cerebral blood vessels dilate, increasing cerebral blood flow and cerebrospinal fluid pressure. A maldistribution of cerebral blood flow and altered metabolism can occur; shivering during recovery is

common.

Renal effects: At the level of 1 MAC phthorothanum causes renal blood flow and glomerular filtration to drop to about 50% of normal. These effects are mitigated by adequate hydration.

Hepatic effects: Phthorothanum depresses liver function. This effect is rapidly reversed when administration of the anesthetic is stopped. Hepatic necrosis that cannot be attributed to known etiologies can occur with phthorothanum anesthesia. Two to five days postoperatively an affected patient develops fever, anorexia, and vomiting. This syndrome is known as **phthorothanum hepatitis**. Eosinophilia and biochemical abnormalities characteristic of hepatitis occur.

Muscular effects: Phthorothanum causes skeletal muscle relaxation by both central and peripheral mechanisms. It appears to increase the sensitivity of end-plates to the action of competitive neuromuscular blocking agents. It relaxes uterine smooth muscle. Phthorothanum, like all potent inhalation agents, can trigger malignant hyperthermia, a potentially fatal condition believed to be autosomal dominant, in which, in response to anesthesia, a sudden, rapid rise in body temperature and signs of increased muscle metabolism occur.

Approximately 70% of phthorothanum is eliminated unchanged in exhaled gas in the first 24 hours after administration; approximately 5% is biotransformed by the cytochrome P-450 system in the endoplasmic reticulum of the liver.

Therapeutic uses: Phthorothanum is a highly potent, nonflammable general anesthetic with a relatively high blood gas partition coefficient. Thus, induction of and recovery from anesthesia with this agent may be prolonged. Phthorothanum is not irritating to the larynx, and thus, induction of anesthesia with this agent is smooth and bronchospasm is not common. Phthorothanum administration is often supplemented with thiopental for induction of anesthesia. Nitrogenum oxydulatum, oxygen, and muscle relaxants are normally used with phthorothanum. Phthorothanum is a safe anesthetic for children.

Enfluranum causes mild stimulation of salivation and tracheobronchial secretions. It suppresses laryngeal reflexes.

Pharmacologic and Respiratory effects: Enfluranum produces dose-dependent respiratory depression. With enfluranum respiratory responses to hypoxia and hypercapnia are less than with phthorothanum. Enfluranum causes bronchodilatation and inhibits bronchoconstriction. **Cardiovascular effects:** Dose-dependent depression of the arterial blood pressure and depressed baroreceptor responses are similar to those caused by phthorothanum. Dose-dependent myocardial depression also occurs and is similar to that caused by phthorothanum. Bradycardia usually does not occur with enfluranum and cardiac output is not decreased as much as with phthorothanum. Enfluranum causes a lower incidence of arrhythmias and less sensitization of the myocardium to catecholamines than phthorothanum does.

The CNS effects: enfluranum anesthesia can lead to an electroencephalographic pattern characteristic of seizure activity or to frank seizures. The seizures are self-limited and can be prevented by avoiding both high concentrations of enfluranum and hyperventilation, which leads to hypocapnia. Enfluranum is contraindicated in patients who have known seizure disorders. Enfluranum causes cerebral vasodilation and increased intracranial pressure as long as the arterial blood pressure remains normal.

Renal effects: Enfluranum anesthesia may cause a reduction in renal blood flow and glomerular filtration which is similar to that caused by phthorothanum.

Hepatic effects: liver impairment is reversible.

Muscular effects: enfluranum provides adequate muscular relaxation for most surgical procedures. The agent acts directly on the neuromuscular junction. Enfluranum relaxes uterine smooth muscle.

Approximately 80% of enfluranum is eliminated unchanged as expired gas. About 5% of enfluranum is metabolized in the liver. Free fluoride ion is released.

Therapeutic uses: Enfluranum is a potent general anesthetic which causes a lower incidence of arrhythmias than phthorothanum. Enfluranum is a better skeletal muscle relaxant than phthorothanum but, unlike phthorothanum, can cause seizure activity.

Isofluranum is the anesthetic of choice among dialkyl-haloethers.

Pharmacologic effects: Isoflurane is an isomer of enflurane and has similar physical properties. It produces significant respiratory depression. Because of hypercapnia resulting from respiratory depression, cardiac output may increase. Peripheral vascular resistance is decreased by isoflurane, resulting in a fall in arterial blood pressure. Isoflurane does not sensitize the heart to catecholamines and rarely causes cardiac arrhythmias. It is a better muscle relaxant than either phthorothane or enflurane.

Therapeutic use: Unlike enflurane isoflurane does not cause seizure activity; unlike phthorothane, isoflurane does not sensitize the myocardium to epinephrine or induce arrhythmias.

Nitrogen oxide is the most active and less dangerous general anesthetic. It is not effective for anesthesia as a single agent because it does not cause deep anesthesia, combine with other general anesthetics, opioids etc. When nitrogen oxide is combined with more potent inhalation agents, such as enflurane or phthorothane, it provides significant analgesia.

Pharmacologic and Respiratory effects: The effects of nitrogen oxide on respiration are minimal.

Cardiovascular effects: When nitrogen oxide is combined with a potent inhalation anesthetic, activation of the sympathetic nervous system results; blood pressure and total peripheral vascular resistance rise, and cardiac output is reduced. Nitrogen oxide is eliminated primarily as an expired gas.

Therapeutic uses: Nitrogen oxide is an important and powerful **analgesic** which is well-tolerated. Its onset of action is rapid, as is recovery from its effects.

Adverse effects: Because of its high partial pressure in blood and its low blood: gas partition coefficient, nitrogen oxide diffuses into air-containing body cavities and may increase the pressure or expand the volume of gas in air pockets. This action can result in: distention of the bowel; expansion or rupture of a pulmonary cyst; rupture of the tympanic membrane in an occluded middle ear; when nitrogen oxide is dissolved in blood, it can enlarge the volume of air emboli.

Diffusion hypoxia can occur at the termination of nitrogenous oxide anesthesia if a patient abruptly begins to breathe room air. Nitrogenous oxide is associated with a high incidence of postoperative nausea and vomiting. Inactivation of vitamin B₁₂ can occur. Leucopenia has been reported with chronic nitrogenous oxide abuse. Nitrogenous oxide is contraindicated in pregnant women, immunosuppressed patients, and patients with pernicious anemia. Now in some clinics **gas xenon** is used. It is more active and less dangerous.

Intravenous anesthetics

Neuroleptanesthesia. When a neuroleptic agent is combined with a powerful narcotic, neuroleptanalgesia is produced. The addition of nitrogenous oxide and oxygen to this combination produces neuroleptanesthesia. The agents most frequently used to achieve neuroleptanalgesia are droperidol.

Drugs for noninhalant narcosis

Ketamine produces a state in which a patient remains conscious but has marked catatonia, analgesia, and amnesia. Ketamine is an antagonist of glutamic acid, blocking the actions of this excitatory transmitter at its NMDA receptor. The drug is a cardiovascular stimulant, and this action may lead to an increase in intracranial pressure. Emergence reactions, including disorientation, excitation, and hallucinations, which occur during recovery from ketamine anesthesia can be reduced by the preoperative use of benzodiazepines. It has no effect on laryngeal reflexes. Skeletal muscle tone, heart rate, arterial blood pressure, and cerebrospinal fluid pressure can be increased by ketamine. The respiratory cycle is maintained near normal.

Therapeutic uses: Premedication with atropine reduces salivary secretions. Premedication with a narcotic analgesic decreases the dose of ketamine needed for anesthesia. **Adverse effects:** Because of its hallucinogen-like structure, **ketamine** frequently produces unpleasant sleep, especially in adults. Recovery from ketamine anesthesia is often accompanied by emergence delirium and psychomotor activity. **Barbiturates** have high lipid solubility

Thiopentalum-natrium is a barbiturate the most frequently used for general

anesthesia. It provides a rapid and pleasant induction and, thus, is often used before administration of stronger agents. It can be used alone to provide anesthesia for a short procedure but thiopentalum-natrium and other barbiturates are poor analgesics. It may accumulate in cellular tissues and has myorelaxant properties. These agents are used for induction of anesthesia and for short surgical procedures. Their anesthetic effects are terminated by redistribution from the brain to other tissues, but hepatic metabolism is required for their elimination from a body. They are respiratory and circulatory depressants because they depress cerebral blood flow. They can also decrease intracranial pressure.

Propofolium is a short-acting intravenous anesthetic which can be used for induction anesthesia or maintenance as part of a balanced anesthesia regimen. Propofolium produces anesthesia at a rate similar to that of the intravenous barbiturates and recovery is more rapid. Propofolium has antiemetic actions and recovery is not delayed after prolonged infusion. The drug is commonly used as a component of balanced anesthesia and as an anesthetic in outpatient surgery. Propofolium may cause marked hypotension during induction of anesthesia, primarily through decreased peripheral resistance. Total body clearance of propofolium is greater than hepatic blood flow, suggesting that its elimination includes other mechanisms in addition to metabolism by liver enzymes. Onset of unconsciousness occurs within 1 minute and duration of action is only 3-5 minutes due to a rapid redistribution. The clarity of mental status upon recovery makes propofolium particularly useful for ambulatory surgical patients. **Pharmacologic effects:** Hemodynamic and respiratory effects are similar to those occurring with barbiturate induction. **Adverse effects:** Hypotension can be particularly severe in older patients.

Midazolamum is a parenteral benzodiazepine used for sedation during short procedures, sedation before general anesthesia, induction of general anesthesia, and as a hypnotic drug in balanced anesthesia regimens. Medazolamum is three to four times as potent as diazepamum, but unlike diazepamum, it does not cause local irritation after intramuscular or intravenous injection. **Pharmacokinetics:** It is highly lipid soluble and rapidly crosses the blood-brain barrier. It is metabolized in

the liver and has a half-life of 1–4 hours. **Adverse effects:** It may cause respiratory depression and anterograde amnesia lasts for at least 2 hours.

Etomidatum is an ultra-short-acting hypnotic used for induction of anesthesia. Cardiovascular effects are virtually absent. **Adverse effects:** Pain on injection; myoclonic movements; postoperative nausea and vomiting, especially with opioid use, are common adverse effects.

Natrii oxybutiras is a synthetic analogue of natural metabolite GABA which penetrates across haemato-encephalic barrier. It has narcotic, analgetic, myorelaxant, nootropic, hypnotic, anticonvulsant, and tocolytic properties.

Therapeutic uses: Narcoses, **seizures**, treat of pregnancy interrupting, as hypnotic and sedative drug.

Adverse effects: Depression of breathing and excretion of cilium.

Propanididum causes short-term narcosis during 5-10 minutes, has analgesic effect, but increases skeletal muscles tonus (stimulates M-cholinoreceptors).

Adverse effects: Nausea, vomiting, headache, salivation, anaphylactic shock (liberator of histamine), hyperpnoea, and apnea.

№	Drug	Drug forms
1.	Phthorothanum	50ml
2.	Enfluranum	250 ml
3.	Propanididum	Amp. 5% 10 ml
4.	Propofolum	Amp. emuls. 1% 20 ml
5.	Isofluranum	100 ml
6.	Thiopentalum- Natrium	0,5; 1
7.	Ketaminum	1% - 20ml 5% - 10ml
8.	Natrii Oxybutras	Amp. 20% - 10ml; 5% - 400ml

Spiritus aethylicus

Spiritus aethylicus has narcotic type of action and antiseptic properties. Antiseptic action is connected with denaturation of microbic cells proteins. Locally spiritus aethylicus is used to clean hands of surgeon and operation field. Spiritus aethylicus resorbitive action is connected with influence at all organs and systems. The influence on the CNS has three stages: excitation, narcosis, paralysis. Spiritus aethylicus stimulates and then oppresses respiratory and vascular moving center. Spiritus aethylicus causes first tachycardia then bradycardia, increases arterial pressure then decreases arterial pressure, activates saliva and stomach glands, in high concentrations spiritus aethylicus decreases stomach moving. **Therapeutical uses:** Spiritus aethylicus is used as antishock, hypnotic, sedative drugs. It is administered intravenously in the case of methyl alcohol intoxication because of inhibition of biotransformation into very toxic methyl aldehyde.

Acute intoxication of spiritus aethylicus is observed when its concentration in blood plasma consists of 3-4 g/l. **Treatment of intoxication** is begun from artificial breathing – artificial ventilation of lungs. Sometimes analeptics are administered. If a patient is in conscious he may be given Sol. Ammonii caustici. It is necessary to make a stomach lavage and give symptomatic drugs (cardio-vascular, antiemetic). Patients must be kept in warm. Under chronic intoxication all organs and systems are suffered, especially the CNS. Delirium tremens may be observed. Peripheral innervations is also damaged. It is stated the damage of intrinsic organs – chronic gastritis, hepatic cirrhosis, lipid dystrophy of liver, heart, and kidneys. It develops psychotic and physic dependence. Alcoholism is gradually cured in a clinic. Disulphyramum (teturamum) is administered during 7 days, then a patient takes 30-40 ml of 40% spiritus aethylicus. Mechanism of action is connected with blockade of aldehyddehydrogenase delary of metabolism of acetaldehyde. A patient feels aversion for alcohol. Effect is not long. Disulphyramum of prolonged action (Esperal) is hemmed under skin.

Hypnotics

There are compounds of different chemical structures which cause hypnosis as

physical sleeping.

There is a chemical classification of hypnotics:

1. Hypnotics with narcotic type of action;

1.1 Barbiturates – Phenobarbitalum;

1.2 The aliphatic compounds – chlorali hydras, bromisovalum;

2. Hypnotics with nonnarcotic type of action;

2.1 Benzodiazepines – nitrazepamum, diazepamum, phenazepamum and others;

2.2 Cyclopyrrolidones' derivatives – zopiclonum;

2.3 Imidazopyrrolidines' derivatives – zolpidemum;

2.4 Aethanolamines derivatives – donormylum;

3. Metabolic drugs ;

3.1 GABA derivatives – natrii oxybutyras, phenibutum;

3.2 Melatoninum.

Barbiturates

Classification: Barbiturates are classified on the basis of their onset and duration of action. **Short-acting** barbiturates (e.g. **thiopentalum-natrium**) act within seconds, and their duration of action is 30 minutes. Their principal use is as intravenous adjuvants to anesthesia. **Long-acting** barbiturates (e.g. **phenobarbitalum**) have duration of action 8 hours. They are effective hypnotics and sedatives and at low doses are used as antiepileptic agents. They are likely to cause hangover. Nowadays only phenobarbitalum is used in clinical practice.

Mechanism of action: Barbiturates interact with barbiturate receptors, which are situated on a complex receptor-ion channel. When the GABA receptors are activated, chloride channels open. Chloride enters the cell, hyperpolarizes it, and produces decreased excitation. Barbiturates depress neuronal activity in the midbrain reticular formation, facilitating and prolonging the inhibitory effects of the GABA and glycine. They may also block the excitatory transmitter glutamic acid, and, at high concentration, sodium channels. Barbiturates are less selective than benzodiazepines, which also have GABA-like actions, because elevating the dose of barbiturates

produces a generalized CNS depression in addition to selective depression at synaptic sites.

Pharmacokinetics: Phenobarbitalum is absorbed from a stomach, small intestine. Phenobarbitalum readily crosses a placental barrier, and concentrations in the fetal blood approach those in maternal, blood. Phenobarbitalum does not connect with albumins of plasma. Phenobarbitalum is not biotransformed. Phenobarbital and their metabolites are principally excreted via the renal route. If renal function is impaired, barbiturates can cause severe CNS and cardiovascular depression. Alkalinization of the urine profoundly expedites the excretion of phenobarbitalum.

Pharmacologic effects: Barbiturates depress the CNS at all levels in a dose-dependent fashion. A barbiturate plus another CNS depressant (e.g. a phenothiazine, ethanol, or antihistamine) can result in the marked depression. Barbiturates have sedative, hypnotic, antiepileptic, spasmolytic, and hypertensive effects. As hypnotics they decrease the amount of time spent in fast sleep. As sedative doses phenobarbitalum has little effect on a cardiovascular system. Toxic dose levels can cause circulatory collapse. Phenobarbitalum is capable of inducing a hepatic microsomal drug-metabolizing enzyme system. This results in an increased degradation of the phenobarbitalum, ultimately leading to barbiturate tolerance. It also causes an increased inactivation of other compounds, such as the anticoagulants, dipheninum, digitoxinum, theophyllinum, and glucocorticoids, leading to potentially serious problems with drug interactions.

Therapeutic uses: Due to their rapid onset of action, phenobarbitalum is used in the emergency treatment of convulsions as in status epilepticus, that is why the benzodiazepines and the similar drugs are the remedies of choice as hypnotics.

Adverse effects: Depressant effects include oversedation and a decrease in fast sleep. Skin eruptions and porphyria may occur. Physiologic as well as psychological dependence may also occur. Grand mat seizures, severe tremors, vivid hallucinations, and psychoses may be observed. Phenobarbitalum excretes vitamins C, B_C, D, that is why it may lead to anemia, osteoporosis, and hemorrhage. An overdose can result in coma, diminished reflexes (although deep tendon reflexes are

usually intact), severe respiratory depression, hypotension leading to cardiovascular collapse, and renal failure.

Aliphatic compounds

Chlorali hydrates

Pharmacokinetics: Chlorali hydras is metabolized in the liver by alcohol dehydrogenase to trichloroethanol, which is thought to be the active metabolite producing the CNS effects. It enhances the ability of hepatic microsomes to metabolize drugs. Trichloroethanol and, to a lesser extent, chlorali hydras are oxidized to trichloroacetic acid, which is excreted in the kidney as the glucuronide conjugate. Chlorali hydras is used as anticonvulsant.

Adverse effects: Chlorali hydras is quite bad tasting and is irritating to the gastrointestinal tract. It has toxic effects on cardio-vascular system, liver, and kidney.

Bromisovalum is used seldom as an oral hypnotic and sedative drug. It is absorbed from the gastrointestinal tract.

Benzodiazepine derivatives. The benzodiazepines at present are generally considered to be good drugs for sedation-hypnosis. In contrast to the various other sedative-hypnotics, the benzodiazepines are not general neuronal depressants. They act on the allosteric site of the GABA receptor (benzodiazepine receptors, which are present in many brain regions, including the thalamus, limbic structures, and the cerebral cortex) facilitating chloride entry into the neuron, which produces an inhibitory effect on a neuronal conduction. Benzodiazepines increase the frequency of the GABA-mediated chloride ion channel opening. **Flumazenil** reverses the CNS effects of benzodiazepines and is classified as an **antagonist** of benzodiazepine receptors.

Nitrazepamum

Pharmacologic effects: Nitrazepamum produces hypnotic effects within 20-40 minutes after an oral dose, which may last for 6-8 hours. It may also cause muscle relaxation. The major metabolite has a long half-life and may cause daytime sedation and motor impairment. Diazepamum, chlozepidum, phenazepamum, lorazepamum

etc. have also long hypnotic effect. The hypnotics **zolpidemum** and **zopiclonum** appear to exert their CNS effects via interaction with certain benzodiazepine receptors, classified as omega subtypes, their CNS depressant effects are antagonized by flumazenil. Duration of its action is 6-8 hours. They do not influence fast hypnosis, have hypnotic effect which is similar to physiological sleeping. Zopiclonum has also psychotropic effect. The dependence liability of zolpidemum and of zopiclonum may be less than that of the benzodiazepines. Zolpidemum and zopiclonum appear to cause less daytime cognitive impairment than most benzodiazepines and have minimal effects on sleep patterns. Alprazolamum and clonazepamum have greater efficacy than other benzodiazepines in panic and phobic disorders. The anxiolytic effects of buspirone occur without sedation or cognitive impairment but take a week or more to develop. The derivatives of aethanolamines (**donormylum**) is H₁-receptors' blocker. It has also hypnotic, sedative, and M-cholinoblockers effects.

Therapeutic use: Benzodiazepines, including nitrazepamum, estazolamum, flurazepamum, and triazolamum, are widely used in primary insomnia and for the management of certain other sleep disorders. Certain benzodiazepines (e.g. diazepamum, midazolamum) are used as components of anesthesia protocols. Special uses include the management of seizure disorders (e.g. clonazepamum) and muscle spasticity (e.g. diazepamum). Longer-acting drugs (e.g. chlozepidum, diazepamum) are used in the management of withdrawal states in persons physiologically dependent on ethanol and other sedative-hypnotics. Zolpidemum, zopiclonum, and donormilum are used only as hypnotics.

Adverse effects: Nitrazepamum causes suppression of fast sleep as other benzodiazepines. Drowsiness, excessive sedation, impaired coordination, confusion, memory lost, and drug dependence may be observed. Zolpidemum, zopiclonum, donormilum have less adverse effects.

№	Drug	Drug forms
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1.	Phenobarbitalum	Pulv.; Tab. 0,05, 0,1
2.	Aethaminalum-Natrii	Pulv.; Tab. 0,1
3.	Nitrazepamum	Tab. 0,005, 0,01
4.	Chlorali Hydras	Pulv. 0,5-1,0 (hypnotics), 2,0-4,0 (anticonvulsant)
5.	Zolpidemum	Tab. 0,01
6.	Zopiclonum	Tab. 0,0075
7.	Bromisovalum	Tab. 0,3
8.	Donormilum	Tab. 0,015

Antiepileptic drugs

Epilepsy comprises a group of chronic syndromes which involve the recurrence of seizures, i.e. limited periods of abnormal discharge of cerebral neurons. Several chemical subgroups of antiseizure drugs are structurally related; these include **hydantoins** (e.g. dipeninum), **barbiturates** (e.g. phenobarbitalum), and **succinimides** (e.g. ethosuximidum). There are several unrelated subgroups, including two tricyclic compounds, **carbamazepinum and oxcarbazepinum**; **natrii valproas**, a carboxylic acid; **benzodiazepinum** (e.g. diazepamum, clonazepamum); **felbamatum**, a carbamatum; **GABA derivatives** (e.g. gabapentinum, vigabatrinum); **lamotriginum**, a phenyltriazinum; and **topiramatum**, a substituted monosaccharide etc. Subgroups of antiseizure drugs are selective in their therapeutic effects for specific types of seizures.

There are anticonvulsant drugs of different actions:

I. Common action for cure acute convulsion of different etiology:

1. General anesthetic (phthorotanium, natrii oxybutyras);
2. Hypnotic drugs (chlorali hydras);
3. Tranquilizators (diazepamum);
4. Neuroleptics (aminazinum);
5. Magnesii sulfas;
6. Myorelaxants (as helping agents);

II. Specific drugs:

1. Drugs for treatment epilepsy ;
2. Drugs for treatment Parkinson disease.

Mechanisms of Action: The general effect of antiseizure drugs is to suppress repetitive action potentials in epileptic foci in the brain. Different mechanisms are involved in achieving this effect. At therapeutic concentrations dipheninum, carbamazepinum, and lamotriginum block voltage-gated **sodium channels** in neuronal membranes. This action results in prolongation of the inactivated state of the Na⁺ channel and the refractory period of the neuron. Phenobarbitalum and natrii valproas may exert similar effects with high doses. Benzodiazepines interact with specific receptors on the GABA_A receptor-chloride ion channel macromolecular complex. In the presence of benzodiazepines, the frequency of chloride ion channel opening is increased; these drugs facilitate the inhibitory effects of the GABA. Phenobarbitalum also enhances the inhibitory actions of the GABA but interact with a different receptor site on chloride ion channels which results in an increased duration of chloride ion channel opening. The GABA transaminase is irreversibly inactivated by vigabatrinum at therapeutic plasma levels and can also be inhibited by natrii valproas at very high concentrations. Inhibition of the GABA transaminase is presumed to enhance the effects of the GABA at synaptic sites. Tiagabinum inhibits the GABA transporters in neurons and glia. Gabapentin is a structural analogue of the GABA, but it does not activate GABA receptors directly. Ethosuximidum inhibits low-threshold (T-type) Ca²⁺ currents, especially in thalamic neurons which act as pacemakers to generate rhythmic cortical discharge. A similar action is reported for natrii valproas. Natrii valproas causes neuronal membrane hyperpolarization possibly by enhancing K⁺ channel permeability. Phenobarbitalum also acts as an antagonist at some glutamate receptors. Topiramatum appears to block sodium channels and potentiate the actions of the GABA. It may also block glutamate receptors.

Therapeutic uses: Diagnosis of a specific seizure type is important for prescribing the most appropriate antiseizure drug (or combination of drugs). Natrii

valproas, carbamazepinum, and dipheninum are the drugs of choice for generalized tonic-clonic (grand mal) seizures and for most cases of simple and complex partial seizures. Phenobarbitalum is now considered to be an alternative agent in adults but continues to be a primary drug in infants. Lamotriginum is also an alternative agent, but its usefulness is limited by its toxic potential. Gabapentinum may be used adjunctively in refractory cases. Topiramatum is approved for adjunctive use with other agents in partial seizures and vigabatrinum may also be useful as a backup drug. Ethosuximidum and natrii valproas are used in absence seizures and are the preferred drugs since they cause minimal sedation. Ethosuximidum is often used in uncomplicated absence seizures if patients can tolerate their gastrointestinal side effects. Natrii valproas is particularly useful in patients who have concomitant generalized tonic-clonic or myoclonic seizures. Clonazepamum is effective as an alternative drug but has the disadvantages of causing sedation and tolerance. Myoclonic seizure syndromes are usually treated with natrii valproas. Clonazepamum can be effective but high doses required cause drowsiness. Lamotriginum is effective in myoclonic syndromes in children. Felbamatum has been used adjunctively with primary drugs but has hematotoxic and hepatotoxic potential. Intravenous diazepamum or lorazepamum is usually effective in terminating attacks of status epilepticus and providing short-term control. For prolonged therapy intravenous dipheninum is usually employed since it is highly effective and less sedating than benzodiazepines or barbiturates. Dipheninum may cause cardiotoxicity (perhaps due to its solvent propylene glycol). Phenobarbitalum has also been used in status epilepticus, especially in children. In very severe status epilepticus general anesthesia may be used. Several antiseizure drugs are effective in the management of bipolar affective disorders, including natrii valproas, carbamazepinum, dipheninum, and gabapentinum. Carbamazepinum is the drug of choice for trigeminal neuralgia. Gabapentinum has efficacy in pain of neuropathic origin and, like dipheninum, may have some value in migraine.

Dipheninum. Pharmacokinetics: Dipheninum acts by stabilizing membranes by decreasing Na^+ conductance during high-frequency repetitive firing. Dipheninum

exerts its dampening effect only when neuronal activity is abnormally high. It allows the normal conduction of action potentials but halts seizure activity. Dipheninum is a weak acid, its intestinal absorption is variable, incomplete, and slow. Nearly all (90%) is bound to plasma protein. The drug is metabolized by the microsomal system and is excreted first in the bile and then in the urine.

Pharmacodynamics: Ipheninum has anticonvulsant and antiarrythmic effects.

Therapeutic uses: Dipheninum is used in the treatment of grand mal epilepsy and tonic-clonic seizure disorders. Its use is contraindicated in liver disease and in patients with absence seizures (petit mal epilepsy) or with convulsions resulting from fever or barbiturate withdrawal.

Adverse effects: Gastrointestinal irritation may occur; thus, the drug should be taken with meals. The following effects may also occur: ataxia, diplopia, blood dyscrasias, hypersensitivity reactions, including the Stevens-Johnson syndrome and systemic lupus erythematosus. Dipheninum should be stopped if a rash occurs. Gingival hyperplasia, hirsutism, increased collagen proliferation, bone growth, hepatitis may be observed. Cardiovascular collapse and the CNS depression may occur with intravenous administration exceeding 50 mg/min. Dipheninum has teratogenic properties.

Succinimides: Ethosuximidum Mechanism of Action. It may involve the release of the GABA.

Pharmacokinetics: Ethosuximidum is absorbed from the gastrointestinal tract. About 80% is metabolized in the hepatic microsomal metabolizing system; 20% is unchanged. Both unchanged drug and hepatic metabolites appear in the urine.

Pharmacodinamics: Ethosuximidum has anticonvulsant and analgetic effects.

Therapeutic uses: Ethosuximidum is considered the drug of the first choice in the treatment of petit mal epilepsy (absence seizures).

Adverse effects: Exacerbates grand mal epilepsy. Gastrointestinal reactions, such as anorexia and nausea. The CNS effects, such as drowsiness, headache, and hiccup; extrapyramidal symptoms and photophobia have also been reported. Hypersensitivity reactions. Psychotic episodes.

Benzodiazepines. Diazepamum, given intravenously, is now considered as a drug of choice for status epilepticus in adults. It should be used with great caution in patients who have received barbiturates. It is also effective against all other types of seizures, particularly petit mal and other minor motor seizures. Its usefulness as a long-term antiepileptic agent is limited by the development of refractoriness within a few months. **Clonazepamum** is useful in the treatment of absence seizures and myoclonic seizures in children. It is absorbed well from the gastrointestinal tract and its central effects develop rapidly. Its chief therapeutic limitation is the development of tolerance, which can be overcome by increasing a dose. At higher doses, however, sedation is induced.

Carbamazepinum is an iminostilbene and is related chemically to tricyclic antidepressants.

Pharmacodynamics: carbamazepinum has anticonvulsant, antidepressant, and analgesic effects.

Therapeutic use: it is used in the treatment of grand mal epilepsy, often as an adjunct to dipheninum therapy. Its anticonvulsant actions are similar to those of dipheninum. Other uses include the treatment of trigeminal neuralgia and occasionally the treatment of bipolar illness. Chronic use results in induction of drug-metabolizing enzymes, thereby reducing serum levels.

Adverse effects: Diplopia, ataxia, and nausea, bone marrow depression, including aplastic anemia, congestive heart failure, atropine-like symptoms, kidney and liver toxicity may occur.

Natrii valproas (dipropylacetic acid) is used as a solvent in the screening of certain compounds for antiepileptic activity. It has antiseizure activity.

Therapeutic uses: Natrii valproas has proved to be the most effective in seizure states with a subcortical focus (e.g. absence seizures). It has also been somewhat effective in grand mal seizures but much less effective in partial seizures.

Pharmacokinetics: Natrii valproas is rapidly absorbed from the gastrointestinal tract. Its mechanism of anticonvulsant action is to involve inhibition of the GABA transaminase, the enzyme responsible for the breakdown of the GABA;

inhibits succinic aldehyde dehydrogenase.

Pharmacodynamics: Natrii valproas has anticonvulsant, psychotonic, antidepressant, and cardioprotective effects.

Adverse effects: The following effects may be observed: teratogenicity, pancreatitis and hepatic failure, especially when the drug is used in combination with other antiseizure medication, anorexia and nausea, sedation and ataxia, alopecia, drug interactions, including a 40% rise in plasma phenobarbital concentration with concurrent administration.

Lamotriginum, vigabatrinum, tiagabinum, and phelbamatum are the drugs of wide spectrum. **Gabapentinum** and **vigabatrinum** are unusual because they are eliminated by the kidney, largely in unchanged form. Lamotriginum is eliminated via hepatic glucuronidation. **Topiramatum** undergoes both hepatic metabolism and renal elimination of intact drug. Adverse effects and complications of the use of these antiseizure drugs are the same as other antiseizure drugs.

№	Drug	Drug forms
1.	Dipheninum	Tab. 0,117
2.	Hexamidinum	Tab. 0,125, 0,25
3.	Natrii Valproas	Tab. 0,15, 0,2, 0,3, 0,5; Caps. 0,15, 0,3
4.	Clonazepamum	Tab. 0,001
5.	Carbamazepinum	Tab. 0,2, 0,4
6.	Ethosuximidum	Caps. 0,25; Flac. 50% - 50ml
7.	Trimethinum	Pulv.
8.	Chloraconum	Tab. 0,25, 0,5
9.	Lamotrigini	Tab. 0,005, 0,025, 0,05, 0,1

Agents used in the treatment of Parkinsonian disorders

The classification of these drugs includes:

I. Drugs which activate dopaminergic system:

- a) precursors of dopamine: levodopa, nacom (levodopa+carbidopa);
- b) dopaminomimetics: bromocriptine, pramipexole etc.;
- c) drugs which increase the release of dopamine and block activity of glutamatergic system: amantadine (amantadine);
- d) inhibitors of the MAO B: selegiline;
- e) inhibitors of the COMT: tolcapone.

II. Drugs which decrease cholinergic activity: cyclohexane, tropicamide, benzerazine.

Parkinsonism is a common movement disorder which involves dysfunction in basal ganglia and associated brain structures. The signs of Parkinsonism include rigidity of skeletal muscles, akinesia (or bradykinesia), flat facies, and tremor at rest. Pathologic characteristics include a decrease in the levels of striatal dopamine and degeneration of dopaminergic neurons in nigrostriatal tract which normally inhibit the activity of striatal GABAergic neurons. The reduction of normal dopaminergic neurotransmission leads to excessive excitatory actions of cholinergic neurons on striatal GABAergic neurons. The main drug that activates dopaminergic system is levodopa.

Levodopa (L-dopa). Mechanism of action. A dopamine deficiency in the striatum needs to be corrected in the treatment of Parkinsonism. Dopamine does not cross a blood-brain barrier; thus, levodopa, the precursor of dopamine, is given instead. Nacom is combination of levodopa and carbidopa. Levodopa is usually given with **carbidopa**, a drug which does not cross a blood-brain barrier but inhibits the DOPA decarboxylase in peripheral tissues. With this combination lower doses of levodopa are effective and there are fewer peripheral side effects.

Pharmacokinetics: Levodopa is well absorbed from a small bowel. However, 95% is rapidly decarboxylated in periphery. Peripheral dopamine is metabolized in the liver to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), which are then excreted in the urine.

Pharmacologic effects: The effects on bradykinesia and rigidity are more

rapid and complete than the effects on tremor. Other motor defects in Parkinson disease are improved. The psychological well-being, memory of a patient is also improved. Salivation and mortality rate are decreased.

Adverse effects: The following defects may be observed: anorexia, nausea, and vomiting upon initial administration, cardiovascular effects, including tachycardia, arrhythmias, and orthostatic hypotension, mental disturbances, including delusions and hallucinations, a decrease in prolactin secretion, dyskinesia upon long-term administration.

Nacom and Sinemet are the trade names of preparations which combines carbidopa and laevodopum in fixed proportions for the most effective treatment of Parkinson's disease. Madopar is a combination of laevodopum and benserisidum, which also blocks decarboxilation of laevodopum.

Adverse effects of the combination are similar to those seen with high doses of laevodopum.

Midantanum. Therapeutic uses and mechanism of action. Midantanum is an antiviral agent used in the prophylaxis of influenza A₂. It was found to improve Parkinsonian symptoms by stimulating the release of dopamine from dopaminergic nerve terminals in the nigrostriatum and delaying its reuptake. Midantanum enhances dopaminergic neurotransmission by glutamate receptors blocking which may involve increasing synthesis or release of dopamine or inhibition of reuptake of it. The drug also has muscarinic blocking actions. Midantanum may be more efficacious in Parkinsonism than the anticholinergic atropine derivatives but is less effective than laevodopum.

Pharmacokinetics: Midantanum is well absorbed orally and is excreted unchanged in the urine.

Adverse effects are infrequent. However, long-term use can produce livedo reticularis in the lower extremities. Tolerance is observed in 6-8 weeks.

Bromocriptinum. Mechanism of action: An ergot derivative, bromocriptinum mimics the action of dopaminum. Bromocriptinum is expensive but probably provides additional therapeutic benefit when added to laevodopum therapy.

Adverse effects such as hallucinations, hypotension, and livedo reticularis are more common with bromocriptinum than with laevodopum. However, it induces less dyskinesia than laevodopum.

Pramipexolum and ropinirolum are recently introduced dopamine receptor agonists; they are not ergot derivatives. These drugs are as effective as bromocriptinum and do not cause side effects typically associated with the use of ergots. They are presently considered to be first-line drugs in the initial management of Parkinson's disease. Dyskinesias, postural hypotension, lassitude, sleepiness, and fatigue have been reported.

Anticholinergic agents decrease the excitatory actions of cholinergic neurons on cells in the striatum by blocking muscarinic receptors.

Pharmacologic effects: Drugs such as cyclodolum, troparinum, brinerdinum may improve the tremor and rigidity of Parkinsonism but they have little effect on bradykinesia. They are used adjunctively in Parkinsonism; they also alleviate reversible extrapyramidal symptoms caused by antipsychotic drugs.

Therapeutic uses: While not as effective as laevodopum or bromocriptinum, anticholinergic agents may have an additive therapeutic effect at any stage of the disease when taken concurrently.

Adverse effects such as mental confusion and hallucinations due to central muscarinic toxicity, can occur as can peripheral atropine-like toxicity (e.g. cycloplegia, urinary retention, and constipation).

Selegilinum is a selective MAO type B inhibitor also known as deprenylum.

Therapeutic uses: The drug is used concurrently with laevodopum, it also prevents catabolism of dopaminum in the brain.

Adverse effects: MAO-B inhibitors, unlike MAO-A inhibitors used for depression, do not cause hypertension after the ingestion of tyramine-rich food.

Tolcaponum which blocks COMT is an adjunctive agent. There is a combined drug **Stalevo** which consists of laevodopum, carbidopum, entacaponum (an analogue of tolcaponum).

№	Drug	Drug forms
1.	Levodopum	Tab. 0,5, 0,25
2.	Midantanum	Tab. 0,1
3.	Cyclodolum	Tab. 0,001, 0,002, 0,005
4.	Nacom	Tab. №20
5.	Madopar	Caps. №20
6.	Selegilinum	Tab. 0,005
7.	Pramipexolum	Tab. 0,00025, 0,001
8.	Bromocriptinum	Tab. 0,0025; Caps. 0,005, 0,01

Analgesics

There are two types of analgesics: analgesics of central action – narcotic analgesics (morphine hydrochloride etc.), drugs of different groups (amitryptilinum, clofelinum etc.) and analgesics peripheral action – nonnarcotic analgesics (acidum acetylsalicylicum, analginum etc.).

Narcotic analgesics

Analgesia provides relief of pain without loss of consciousness, in contrast to anesthesia. The chief action of opiates and similar synthetic compounds is to impair the normal sensory awareness-and response to tissue injury. Opium is dry juice of *Papaver somniferum* which opiates is derived from the poppy plant. The exudate of the seed capsule contains alkaloids morphin, codein, thebaine, and papaverine. The term opioid or narcotic analgesics refers to both naturally occurring opiates and synthetic drugs with similar actions.

Mechanism of action: Some of the effects of opioid analgesics have been interpreted in terms of their interactions with specific opioid receptors in the CNS and peripheral tissues. Certain opioid receptors are located on primary afferents and spinal cord pain transmission neurons (ascending pathways) and on neurons in the midbrain and medulla (descending pathways) that function in pain modulation. Other opioid receptors that may be involved in altering *reactivity* to pain are located on

neurons in the basal ganglia, the hypothalamus, the limbic structures, and the cerebral cortex. There are four types of opioid receptor: μ , σ , κ , δ .

Mu (μ) and delta (δ) receptors: Activation of mu and delta receptors contributes to analgesia at both spinal and supraspinal levels, to respiratory depression, and to physical dependence which can result from chronic use of some opioid analgesics.

Kappa (κ) receptors: Kappa receptor activation contributes to spinal analgesia and plays a role in sedative effects of opioid drugs.

Opioid receptors are thought to be activated by endogenous peptides under physiologic conditions. These peptides (e.g. enkephalins, dynorphin, beta-endorphin) bind to opioid receptors and can be displaced from binding by opioid antagonists. These peptides function as classic neurotransmitters. They appear to modulate transmission at many sites in the brain and spinal cord and in primary afferents, they have been implicated in hormonal fluctuations, thermoregulation, mediation of stress and anxiety, production of analgesia, maintain homeostasis.

Ionic mechanisms: Opioid analgesics inhibit synaptic activity, partly through direct activation of opioid receptors and partly through release of the endogenous opiopeptins, which are themselves inhibitory to neurons. All three major opioid receptors are coupled to their effectors by G proteins and they activate phospholipase C or inhibit adenylylcyclase. At the postsynaptic level, activation of these receptors opens K^+ ion channels to cause membrane hyperpolarization (inhibitory postsynaptic potentials; IPSPs). At the presynaptic level, opioid receptor activation closes voltage-gated Ca^{2+} ion channels to inhibit neurotransmitter release. Presynaptic actions result in the inhibition of release of multiple neuro-transmitters, including acetylcholine, noradrenalin, serotonin, glutamate, and substance P.

Narcotic analgesics may be classified as **agonists** (receptor activators), partial agonists (activator of concrete receptors) **antagonists** (receptor blockers), or mixed agonist-antagonists.

Morphine hydrochloride is a derivative of the phenanthrene series of opium alkaloids.

Pharmacokinetics: Morphine hydrochloride is not well absorbed from the gastrointestinal tract. The analgesic effect is greater when the drug is administered intramuscularly or intravenously, rather than orally. Morphine hydrochloride is metabolized in the liver, where it is transformed into inactive metabolites by conjugation with glucuronide. It undergoes a significant first-pass effect. Ninety percent of a given dose is excreted in the urine; the remaining 10% is excreted in the faeces. The latter component is derived from bile as conjugated morphine hydrochloride and may be absorbed again.

Pharmacologic and CNS effects: Analgesia and increased tolerance of pain, sedation are the most prominent effects of morphine hydrochloride. Consciousness is not lost and a patient can usually locate the source of pain. Some patients become euphoric. If morphine hydrochloride is given to a person who is pain-free, dysphoria, anxiety, or mental clouding may occur. Some patients experience dysphoria. At higher doses, the drugs may cause mental clouding and result in a stuporous state called narcosis. Morphine hydrochloride stimulates the chemoreceptor trigger zone, producing nausea and vomiting. In most cases, after the first therapeutic dose, subsequent doses of morphine hydrochloride do not cause vomiting. Morphine hydrochloride produces miosis by stimulating the Edinger-Westphal nucleus, and pinpoint pupils are indicative of toxic dosage prior to asphyxia. The miosis can be blocked with atropine sulfate. Morphine hydrochloride is a powerful respiratory depressant, which acts by reducing the responsiveness of the respiratory centers in the brain stem to blood levels of carbon dioxide. Due to the depressed vascular-motor centre respiration and increased arterial carbon dioxide retention, cerebral vasodilatation can occur, causing an increase in intracranial pressure. Morphine hydrochloride is believed to stimulate the release of the ADH, producing oliguria. Morphine hydrochloride is a potent cough suppressant. Morphine hydrochloride has a biphasic, dose-dependent effect on body temperature. Low doses of morphine hydrochloride cause a decrease and higher doses cause an increase in body temperature.

Cardiovascular effects: Orthostatic hypotension can occur due to vasomotor

medullary depression and histamine release.

Gastrointestinal effects: Constipation results from reduced peristalsis and stomach motility. Both biliary and pancreatic secretions are decreased. Constriction at the sphincter of Oddi causes an increase in biliary pressure.

Other systemic effects: Morphine hydrochloride increases detrusor muscle tone in the urinary bladder, producing a feeling of urinary urgency. Vesical sphincter tone is also increased, making voiding difficult. Prolongation of labour can occur by an undefined uterine mechanism. Bronchoconstriction can occur because morphine hydrochloride causes the release of histamine and causes vagal stimulation. Cutaneous vasodilatation secondary to histamine release can result in pruritus and sweating.

Therapeutic use: Analgesia, such as the relief of pain from myocardial infarction, terminal illness, surgery, and obstetrical procedures, is the major use of morphine hydrochloride. It is also used for the acute treatment of dyspnoea due to pulmonary edema, in which morphine hydrochloride produces decreased peripheral resistance and increased capacity of peripheral and splanchnic vascular compartments. Because of their constipating effects, the morphine hydrochloride-like drugs can be useful in treating severe diarrhea.

Adverse effects: Respiratory depression is the most important effect and is dose-dependent. Nausea and sometimes dysphoria can occur. Increased biliary tract pressure can occur, and caution should be exercised in giving opiates to patients with gallbladder disease. Long-term chronic administration can result in physical dependence. Pinpoint pupils are a consistent finding in addiction. Allergic reactions can occur, and skin rashes are a common manifestation. Due to morphine hydrochloride bronchoconstrictive action, the drug is contraindicated for asthmatic patients. **Tolerance** may be developed to analgesia, euphoria, and respiratory depression.

Codeini phosphas is a 3-methyl ether of morphine hydrochloride. It can be obtained from opium or synthesized by methylation of morphine hydrochloride. Although the **pharmacologic effects** of codeini phosphas are similar to those of

morphine hydrochloride, it has about one-twelfth the analgesic potency of morphine hydrochloride and it is generally used for somewhat milder pain. Codeini phosphas has a high oral-parenteral potency ratio when it is administered orally. Codeini phosphas is also very useful as a cough suppressant. Codeini phosphas produces less sedation or respiratory depression than morphine hydrochloride and fewer gastrointestinal effects.

Aethylmorphini hydrochloride is a cough suppressant which is not used in Ukraine.

Omnoponum is a neogallnic drug which contractiles intestine muscle less (contains papaverinum), produces effects similar to those of morphine hydrochloride but with a lower incidence of nausea and vomiting.

Promedolum, a phenylpiperidine derivative, is an entirely synthetic analgesic. Promedolum is well absorbed by all routes of administration. Excretion is mainly in the urine. Promedolum is less active, causes respiratory depression and possesses addiction liability, less severe than in case with morphine hydrochloride. Promedolum does not cause smooth-muscle spasm, including bronchial spasm. It possesses weak, spastic pharmacologic effects to gastrointestinal and biliary tract. It stimulates uterus contraction.

Phentanylum has 80-100 times more analgesic potency and respiratory depressant properties of morphine hydrochloride and is more effective than morphine hydrochloride in maintaining hemodynamic stability. When combined with droperidol, it produces dissociative analgesia or neuroleptanalgesia. Its principal use is in anesthesia, where it is administered parenterally. It has a rapid onset and short duration of action. High doses of phentanylum are capable of producing muscular rigidity. **Sufentanilum** is used as a short-acting anesthetic adjunct; it has a shorter onset of action than phentanylum. **Alfentanilum** is a synthetic opioid analgesic related to phentanylum and sufentanilum. It has a more rapid onset of action and shorter duration of narcotic effect than phentanylum. It is used as an adjunct to general anesthetics and as an anesthetic induction agent. **Methadonum** is a modified diphenylheptane. This synthetic analgesic has pharmacologic properties similar to

those of morphine, but it is more effective when administered orally than morphine hydrochloride. **Nalorphini hydrochloride** is a gonist-antagonist but used as an opioid antagonist. It possesses analgesic properties with less respiratory depression than morphine hydrochloride. Nalorphini hydrochloride can lead to withdrawal symptoms when it is given **to narcotic-dependent patients**.

Pentazocini lactas and hydrochloride is a benzomorphan derivative with moderate agonistic and weak antagonistic activity. Due to its antagonistic activity, pentazocini hydrochloride is capable of precipitating withdrawal in addicts. Although pentazocini lactas is similar to morphine hydrochloride in pharmacologic properties, it has one-fifth the analgesic potency. Pentazocini hydrochloride is well absorbed from the gastrointestinal tract as well as from subcutaneous and intramuscular sites. It is biotransformed in the liver and excreted via the kidney. It has less constrictive effects on intestines, less drugs dependence. It may increase arterial pressure and cause tachycardia.

Adverse effects: Pentazocini hydrochloride can produce psychotomimetic effects, such as anxiety and hallucinations. There may be less nausea associated with its use than with other opioids. Analgesic doses are capable of increasing a pulmonary artery pressure and cardiac work. Respiratory depression with higher doses is less pronounced than with comparable doses of morphine hydrochloride.

Butorphanolum is agonist-antagonist and has actions similar to those of pentazocini hydrochloride and lactas. As with pentazocini lactas but in contrast to morphine hydrochloride, as an analgesic dose is increased, respiratory depression is not increased in proportion. Pulmonary artery pressure and myocardial work are increased at analgesic doses. Unlike pentazocini lactas, butorphanolum does not precipitate a withdrawal syndrome in opioid addicts.

Buprenorphinum is a partial agonist with low potential for abuse. Its onset of action is within 15 minutes when given parenterally. It is metabolized in the liver and excreted in the faeces and urine. A respiratory depression caused by buprenorphinum is quantitatively similar to that caused by morphine hydrochloride. Buprenorphinum can precipitate withdrawal symptoms in narcotic-addicted patients. Its pharmacologic

activity is not easily reversed, even with high doses of naloxoni hydrochloride. It has less drug dependence than morphine hydrochloride, acts slower but longer.

Nalbuphinum, although structurally similar to naloxoni hydrochloride, is equivalent (on a weight basis) to morphine hydrochloride in producing analgesia. It is considered to be a partial antagonist. Although its antagonistic properties are weak, it precipitates withdrawal in the opioid addict.

Nalorphini hydrochloride is an agonist-antagonist. It is used as antidotum to morphine hydrochloride, but is not recommended as analgetic because of its psychosomimetic effects.

Naloxoni hydrochloride, an N-allyl derivative of oxymorphone, is a complete antagonist. Naloxoni hydrochloride, like other competitive receptor antagonists, blocks opioid receptors. Sedative effects, respiratory depression, and adverse cardiovascular effects of opioid agonists are reversed within 1—2 minutes after parenteral administration of naloxoni hydrochloride. There may be an "overshoot," producing increased respiration for a short period of time. Duration of the antagonistic effect is dose-dependent and usually lasts 1-4 hours. If naloxoni hydrochloride is administered to opioid-addicted patients, a withdrawal syndrome is easily precipitated. Tolerance to the antagonistic effects is not developed. Naloxoni hydrochloride is usually administered parenterally. It is metabolized in the liver via glucuronide conjugation. In obstetrics, mothers who have received opioids during labour may be given a dose of naloxoni hydrochloride just prior to delivery to minimize neonatal respiratory depression. Alternatively, naloxoni hydrochloride can be administered to a neonate via the umbilical vein.

Naltrexonum, another complete antagonist, is now a treatment of choice for patients addicted to heroin or other opioids. It can be administered orally. It has twice as more the potency of naloxoni hydrochloride and three times the duration of action. An opioid abstinence syndrome can result if naltrexone is administered at high doses. Naltrexonum may cause insomnia, anxiety, abdominal cramping, nausea, and joint pain. It is contraindicated in patients with acute hepatitis or hepatic failure.

№	Drug	Drug forms
1.	Morphine Hydrochloride	Tab. 0,01; Amp. 1% - 1ml
2.	Omnoponum	Pulv.; Amp. 1%, 2% - 1ml
3.	Codeine Phosphas	Pulv.
4.	Promedolum	Pulv.; Tab. 0,025; Amp. 1%, 2% - 1ml
5.	Phentanylum	Amp. 0,005% - 2,5ml
6.	Pentazocini hydrochloridum	Tab. 0,05
7.	Buprenorphinum	Tab. 0,0002; Amp. 0,03% - 1ml
8.	Butorphanolum	Amp. 0,5% - 1ml
9.	Pentazocini Lactas	Amp. 3% - 1, 2ml Supp. rect. 0,05
10.	Tramadolum	Caps. 0,05 Amp. 5% - 1, 2ml Supp. rect. 0,1
11.	Nalorphini hydrochloridum	Amp. 0,5% 1ml
12.	Naltrexoni hydrochloridum	Tab. 0,0005
13.	Naloxoni hydrochloridum	Amp. 0,04% - 1ml

Non-narcotic analgesics differ from narcotic analgesics: they have less intensity of analgetic effect; they have cooperative analgetic, antinflamatory,

antipyretic effects; they have no drug dependence, euphoria, abstinence, do not depress respiratory center.

Classification of non-narcotic analgesics is as follows:

1. Derivatives of acidum salicylicum: acidum acetylsalicylicum (aspirin, acelysin) etc.;
2. Derivatives of pyrazolone: analginum (metamizolum), butadionum (phenylbutazonum);
3. Derivatives of anyline: paracetamolum;
4. Derivatives of indolacetic acid: indomethacinum (methinilol), sulindaek (clinoryl);
5. Derivatives of phenylacetic acid diclofenac-natrium (voltaren, ortophen, revodina);
6. Derivatives of antranil acid: acidum mephenamicum (ponstelum, parckemed); acidum fluphenamicum (arlet);
7. Derivatives of propionic acid: iluprophenum (bruphen), naproxenum (naprosine), ketoprophenum (ketonal, fatum), flurbiprophenum (flugalin);
8. Oxymum: pyroxicanum (felden), tenoxicanium (tenoptyl), meloxicanium (movalis), lornoxicamum (xetocam);
9. Derivatives of isonicotine acid: amisonum;
10. Coxibs: celecoxibum (celebrex), rofecoxilum (rofica, aviox) etc.;
11. Derivatives of sulphone acid: nimesulidum (mesulide);
12. Others: acidum niphlumicum (donalginen), ketorolac, diphlunizalum (dolobide) etc.

Non-narcotic analgesics are more effective in case of neurologic pain, e.g. headache etc.

Mechanism of analgetic action: Non-narcotic analgesics disturb synthesis, release and activation of pain mediators (prostaglandins, hystamine, serotonin, quinines); decrease some enzymes activity (proteases); decrease edema, tissues infiltration, pressure on receptors; central component: drugs influence on thalamic nucleuses, inhibit pain, impulses in afferent ways.

Mechanism of antipyretic action: Inhibit cyclooxygenase activity, restoring of normal cerebral neurons; thermoregular activity according to inhibition of prostaglandins synthesis (PGE₂) and decrease its pyrogenic influence, increase widening of skin vessels intensifying sweating.

Mechanism of anti-inflammation action of non-narcotic analgetic and nonsteroid anti-inflammatory drugs. Drugs block cyclooxygenase enzyme activity and inhibit synthesis of prostaglandins endoperoxides, free radicals. The drugs block histidinecarboxylase, triptophandecarboxylase, decrease histamine, serotonin and other biological substances influence. They also stabilize lizosomes membranes, decrease release of enzymes (proteases) inhibit cells reaction on flagogene irritation, formation of complex antigen-antibody. They inhibit formation of the ATP and decrease energetic supply of biochemical processes. These drugs prevent proteins denaturation and have anticomplemental activity. They weaken prostaglandines influence on cells immunity. They decrease capillars permeability and gialuronidase activity. They have antiproliferative action. The salicylates may stimulate glucocorticoids formation, acidum mephenamicum, and amisonum stimulates synthesis of interferonum.

Pharmacology of non-narcotic analgesics (see nonsteroid inflammatory drugs):

№	Drug	Drug forms
1.	Acidum Acetylsaliculicum	Tab. 0,25, 0,5; Tab. 0,075 – 0,325
2.	Analginum	Pulv.; Tab. 0,5; Amp. 25%, 50% - 1, 2ml
3.	Paracetamolium	Tab. 0,2; Ung. 5% - 20,0
4.	Acidum Mephenamicum	Tab. 0,25, 0,35, 0,5
5.	Ibuprophenum	Dragée 0,2

		Tab. 0,2
6.	Diclofenac-natrium	Tab. 0,025 Amp. 2,5% - 3ml
7.	Indomethacinum	Dragée, caps. 0,025; Tab. 0,01, 0,025, 0,1, 0,075; Ung. 10% - 40,0; Supp. rect. 0,05; Caps. 0,02
8.	Meloxicam	Tab. 0,0075, 0,015
9.	Amizonum	Tab. 0,25
10.	Pyroxicamum	Tab. 0,01; Caps. 0,02

Antipsychotic agents

These agents are prescribed for the management of psychotic symptoms; they are sometimes referred to as **major tranquilizers** or **neuroleptics**. They are useful in both acute and chronic psychoses and in nonpsychotic individuals who are delusional or excited. They improve mood and behavior without producing excessive sedation. As a group, these agents produce little physical dependence or habituation but to greater extent they are capable of causing extrapyramidal symptoms, both reversible (Parkinsonian symptoms, akathisia) and irreversible (tardive dyskinesia). The antipsychotic drugs (**neuroleptics**) are effective in controlling many manifestations of psychotic illness. Hallucinations or delusions, may be attenuated by antipsychotic drugs.

The major chemical subgroups of antipsychotic drugs are **phenothiazines** (e.g. aminazinum, thioridazinum, fluphenazinum etc), **thioxanthenes** (e.g. chlorprothixenum), and the **butyrophenones** (e.g. haloperidolum, droperidolum). Several newer drugs of varied **heterocyclic** structure are also effective in schizophrenia, including clozapinum, olanzapine, molindonum, pimozidum, risperidonum, quetiapinum, and sertindolum. In some cases, these atypical antipsychotic drugs have proved to be more effective and less toxic than the older

ones.

Mechanism of action: A dopamine hypothesis of schizophrenia proposes that a disorder is caused by a relative excess of functional activity of neurotransmitter dopamine in specific neuronal tracts in the brain. The therapeutic efficacy of most of the older antipsychotic drugs correlates with their relative affinity for the D₂ receptor. There is also a correlation between blockade of D₂ receptors and extrapyramidal dysfunction. Several newer antipsychotic agents have higher affinities for other receptors than for the D₂ receptor, for example, alpha adrenoceptor-blocking action correlates well with antipsychotic effect for many of the drugs. Clozapine, a drug with significant D₄ and 5-HT₂ receptor-blocking actions, has low affinity for D₂ receptors. Most of the newer atypical drugs (olanzapine, quetiapine, risperidone, and sertindole) have high affinity for 5-HT_{2A} receptors, though they may also interact with D₂ and other receptors. Most of these atypical drugs cause less extrapyramidal dysfunction than standard drugs.

Phenothiazines. Pharmacokinetics: The phenothiazines are erratically absorbed from the gastrointestinal tract. They are highly protein-bound and enter the fetal circulation. Their biologic effect lasts 24 hours, allowing a daily dosing. Phenothiazines are metabolized in a hepatic microsomal system by hydroxylation, followed by conjugation with glucuronic acid. In addition, the formation of sulfoxides is an important metabolic pathway. At least five metabolites ultimately appear in the urine.

Pharmacologic and CNS effects: A psychotic patient has fewer hallucinations and delusions. Improvements in behavior are most often noted with long-term therapy. Tolerance to these effects is rarely seen. The antipsychotic effects are believed to be due to antagonism of dopaminergic neurotransmission in limbic, nigrostriatal, and hypothalamic systems. Extrapyramidal symptoms occur most often with chronic administration. Phenothiazines having the greatest antihistaminic and anticholinergic properties will exhibit the fewest extrapyramidal effects. **Neuroleptic** effects of the antipsychotic drugs consist of emotional quieting, reduced physical movement, and a potential for neurologic side effects. The drugs have little effect on

the intellectual functioning of a patient. Most phenothiazines are antiemetic. In high doses, phenothiazines may directly depress the medullary vomiting center. Phenothiazines are capable of altering temperature-regulating mechanisms. Normally, they produce hypothermia; however, in a hot climate they can cause hyperthermia because of failure to lose body heat. Since phenothiazines depress the hypothalamus, endocrine alterations may occur. This includes the release of lactogenic hormone (prolactin), inducing lactation. Abnormal pigmentation can occur because of an increased release of melanocytestimulating hormone from the pituitary. Increased levels of prolactin may lead to galactorrhea and gynecomastia. Phenothiazines decrease corticotropin release and secretion of pituitary growth hormone. Weight gain and increased appetite are seen with phenothiazine use.

Peripheral effects: An α -adrenergic blocking activity is seen, especially with aminazinum. Adrenergic potentiation, especially with chronic administration, is probably a result of the ability of phenothiazines to inhibit the reuptake of noradrenalinum. Anticholinergic effects can result in blurred vision, constipation, dry mouth, decreased sweating, and, rarely, urinary retention. Miosis is seen with aminazinum and is probably due to α -adrenergic blockade. Other phenothiazines can produce mydriasis. Aminazinum is a potent local anesthetic. Antihistaminic activity is seen with most phenothiazine derivatives. Inhibition of ejaculation without interference with erection can occur, especially with thioridazine. Inhibition of antidiuretic hormone (ADH) secretion by aminazinum can result in a weak diuretic effect. Orthostatic hypotension can occur as a result of both central action of phenothiazines and inhibition of noradrenaline uptake mechanisms. Aminazinum has an antiarrhythmic effect upon the heart. Phenothiazines are known to enhance pharmacologic actions of barbiturates, narcotics, and ethyl alcohol.

Therapeutic uses: Phenothiazines are used chiefly in the treatment of psychotic disorders, including mania, paranoid states, schizophrenia, and psychoses associated with chronic alcoholism (alcoholic hallucinosis). Several phenothiazines have proven effective in the treatment of nausea and vomiting of certain etiologies, such as drug-induced nausea. Aminazinum has proved useful in the control of

intractable hiccup.

Adverse and CNS effects: A Parkinsonian syndrome may occur in which patients display rigidity and tremor at rest. Acute dystonic reactions may be seen with initial drug therapy. Patients display facial grimacing and torticollis. Tardive dyskinesia may be seen with chronic therapy. Patients display sucking and smacking of the lips and other involuntary facial movements. The dyskinesia may persist far after discontinuation of therapy. Lethargy and drowsiness also may occur.

Cardiovascular effects include orthostatic hypotension, which can result in syncope, and reflex tachycardia.

Allergic reactions most often occur during the first few months of therapy. Cholestatic jaundice may occur; it resolves with discontinuation of drug therapy. Blood dyscrasias (e.g. agranulocytosis) and eosinophilia can occur but they are rare. Various forms of dermatitis may occur, including a photosensitivity reaction which resembles a severe sunburn. Somnolence and hypotension are prominent adverse effects of acute intoxication.

Thioxanthene derivatives are similar to the phenothiazine derivatives both chemically and pharmacologically. They differ chemically in that a carbon is substituted by a nitrogen in the central ring of the phenothiazine nucleus. Thioxanthenes in clinical use are **chlorprothixenum** and **flupenthixolum**. **Chlorprothixenum** has prominent antiemetic, anticholinergic, and antidepressant effects.

Butyrophenones: The prototype is **haloperidolum**, which resembles the phenothiazine derivatives pharmacologically. It has potent antiemetic properties, antagonizing stimulation of a chemoreceptor trigger zone. Significant extrapyramidal symptoms are associated with its use. It has no hypertensive effect. Another butyrophenone, **droperidolum**, is often combined with a potent narcotic analgesic, such as fentanyl, to produce neuroleptanalgesia. Droperidolum is used for neuroleptanalgesia, because of its quick effect, short duration of action, myorelaxant, and hypertensive effects. Droperidolum has quick and short effects, produces hypotension and myorelaxantia. **Risperidonum** is more active agent, a derivative of

benzoxazolum.

Clozapinum is a tetracyclic *N*-methyl-piperazinyl-dibenzodiazepine analogue.

Pharmacokinetics: At least 80% of orally administered clozapinum appears in the urine or faeces as metabolites. The $t_{1/2}$ is 12 hours.

Pharmacologic effects: Clozapinum lacks extrapyramidal side effects. It also differs from typical neuroleptic agents due to low affinity for D₁ and D₂ dopamine receptors. It does have relatively potent anticholinergic activity. Other activities include antiadrenergic, antiserotonergic, and possible antihistaminergic activities.

Therapeutic uses: Clozapinum can be effective in treating some patients with psychosis who are not responsive to standard neuroleptic drugs. It can be used safely if granulocyte counts are closely monitored.

Adverse effects: Because of the high risk of potentially fatal agranulocytosis, risk of seizures at high doses, inconvenience of weekly white cell counts.

Olanzapinum is more active agent.

Lithium and other drugs used in bipolar (manic-depressive) disorder

Pharmacokinetics: Lithii carbonas is absorbed rapidly and completely from the gut. The drug is distributed throughout the body water and excreted by the kidneys with a half-life of about 20 hours. Plasma levels should be monitored, especially during the first weeks of therapy, to establish an effective and safe dosage regimen. Plasma levels of the drug may be altered by changes in body water. Thus, dehydration or treatment with diuretics (thiazides) may result in an increase of lithium in the blood to toxic levels. Theophylline increases a renal clearance of lithium.

Mechanism of action: It inhibits a recycling of neuronal membrane phosphoinositides involved in the generation of inositol trisphosphate (IP₃) and diacylglycerol (DAG). These second messengers are important in amine neurotransmission, including that mediated by central adrenoceptors and muscarinic receptors. Competition between lithium and sodium sites may lead to altered neuronal functions.

Therapeutic uses: Lithii carbonas carbonate is used in the treatment of bipolar

affective disorder (manic-depressive disease). Maintenance therapy with lithium decreases manic behavior and reduces both frequency and magnitude of mood swings. Alternative drugs of value in bipolar affective disorder include **carbamazepinum, clonazepamum, gabapentinum, and natrii valproas.**

Adverse neurologic effects of lithii carbonas include tremor, sedation, ataxia, aphasia, thyroid enlargement, and acneiform skin eruptions. The use of lithium during pregnancy may increase the incidence of congenital cardiac anomalies.

№	Drug	Drug forms
1.	Aminazinum	Dragee 0,025, 0,05, 0,1; Amp. 2,5% - 1, 2, 5, 10ml
2.	Triftazinum	Tab. 0,001, 0,05, 0,01; Amp. 0,2% 1ml
3.	Chlorprothixenum	Tab. 0,015, 0,05; Dragee 0,015, 0,05; Amp. 2,5% - 1ml
4.	Haloperidolum	Tab. 0,0015, 0,005; Flac. 0,2% - 10ml; Amp. 0,5% - 1ml
5.	Resperidonum	Tab. 0,001, 0,002, 0,004; Flac. 20 ml, 100 ml
6.	Droperidolum	Amp. 0,25% - 5, 10 ml
7.	Phthorphenazinum	Tab. 0,001, 0,0025, 0,005; Amp. 0,25% - 1ml
8.	Azaleptinum (Clozapinum)	Tab. 0,025, 0,1; Amp. 2,5% - 2ml
9.	Sulpiridum	Caps. 0,05; Amp. 5% 2ml
10.	Lithii Carbonas	Tab. 0,3

Agents used in the treatment of anxiety

Unlike antipsychotic agents, tranquilizers are used to treat anxiety or neurosis. They

are not used in the treatment of psychosis. These drugs are called **anxiolytics, antianxiety, antifobic, tranquilizers or minor tranquilizers**. The tranquilizers are used in the cases of neurotic and borders status.

Chemical classification of tranquilizers:

1. Derivatives of benzodiazepines, chlozepidum (elenium), diazepamum (sibazonum, relanium), phenazepamum, gidazepamum, nozepamum (tazepamum), mezapamum (rudotel), lorazepamum, alprazolamum, tophizopamum etc.;
2. Derivatives of propandiolum: meprobamatum (meprostanum);
3. Derivatives of difenilmetanum: amizylum (benactizinum), hydroxizinum;
4. Drugs of other groups: buspironum, mebicar, trioxasinum, etifoxinum.

Meprobamatum is one of the first tranquilizers (propandiol carbamate). Now it is not a widely used as antianxiety agent; it has been largely replaced by the benzodiazepines.

Benzodiazepines are considered drugs of choice in the treatment of anxiety, partly because of their high therapeutic index. The first benzodiazepine was **chlozepidum**. Others include **diazepamum, clonazepamum, phenazepamum, lorazepamum, oxazepamum, gidazepamum, prazepamum, alprazolamum**, the anesthetic **midazolamum**, and the sedative-hypnotics **flurazepamum, triazolamum, and temazepamum**.

Pharmacokinetics: Diazepamum, flurazepamum are relatively rapidly absorbed, while oxazepamum, prazepamum, and temazepamum are more slowly absorbed. Triazolamum, midazolamum, alprazolamum, and clonazepamum have an intermediate onset of action. All benzodiazepines are soluble in lipids and cross the blood-brain barrier. Plasma levels reflect brain levels. Benzodiazepines are metabolized primarily by microsomal oxidation and glucuronide conjugation.

Mechanism of action: Benzodiazepines connect with benzodiazepine receptors, which are fragments of the GABA receptors and chloride canals fragments. Benzodiazepines potentiate the binding of the GABA to receptors, intensify chloride influx.

Pharmacologic effects: These drugs have **anxiolytics, antianxiety, antifobic**

properties. Tranquilizers, antianxiety agents have sedative and even hypnotic properties and also possess some central skeletal muscle relaxant activity. They have a habituation and physical dependence liability. Tranquilizers are psychotropic drugs which decrease fear, anxiety, uneasiness, and intrinsic tension. At therapeutic doses the benzodiazepines have minimal effects on the cardiovascular system. The benzodiazepines, especially diazepamum has myorelaxants action.

Therapeutic uses: They may be used for treatment of anxiety. Because they increase the seizure threshold, benzodiazepines are useful as anticonvulsants, especially diazepamum in case of status epilepticus. Benzodiazepines (nitrazepamum, flurazepamum, temazepamum, and triazolamum) are also effective as hypnotics. Midazolamum is used for anesthetic premedication. Diazepamum is a parenteral benzodiazepine which may have preoperative use). Benzodiazepines may be used as amnestics, e.g. in cardioversion and as sedative, treatment of alcohol withdrawal syndromes, as central skeletal muscle relaxants, and for treatment of nightmares.

Adverse effects: The following effects may occur: ataxia, drowsiness, and sedation (additive depressant effects are seen when benzodiazepines are combined with other agents possessing the CNS depressant activity), paradoxical increased anxiety, including psychoses, especially with high doses, reversible confusion in the elderly, menstrual irregularities, including anovulation, overdoses, although frequent, are seldom fatal. Treatment is supportive. Due to high plasma-protein-binding characteristics of benzodiazepines the benefit from dialysis is limited. Withdrawal symptoms are influenza-like muscle aches and nausea. These symptoms are rare, except in the case of alprazolam. Agent-specific effects include: triazolamum may cause rebound insomnia; lorazepamum and triazolamum have a greater risk of inducing amnesia.

Buspironum is an antianxiety agent which is not chemically or pharmacologically related to benzodiazepines, barbiturates, or other sedative-anxiolytic drugs. Buspironum can connect dopamine and serotonin receptors.

Therapeutic uses: Buspironum is used for a short-term treatment of generalized anxiety. It may require 1-2 weeks for a therapeutic effect to take place.

Adverse effects include restlessness and dysphoria with high doses. Buspironum is appreciably free of other adverse effects. It has little potential for abuse.

There are day-time tranquilizers which do not provoke hypnotic effect (mebicar, gidazepamum, oxazepamum, and trioxazinum).

	Drugs	Drug forms
	Chlozepidum	Tab. 0,005
	Phenazepamum	Tab. 0,00025 – 0, 001
	Diazepamum (Sibazonum)	Tab. 0,005; Amp. 0,5% - 2ml
	Mezapamum	Tab. 0,01
	Gidazepamum	Tab. 0,02, 0,05

Sedative Drugs

Sedative drugs are the group of drugs which exert calmative action due to decrease of the processes of internal inhibition, which leads to the predominance of inhibition upon excitation in the CNS. In contrast to tranquilizers sedative drugs do not eliminate negative emotions (internal tension, anxiety, fear, etc.). They do not provide a myorelaxation action and do not potentiate effects of other neurotropic drugs. They also do not cause drug dependence. This group of drugs is used in low neuroses, increased irritability, and insomnia. Sedative drugs include several groups: 1. bromides — natrii bromidum, kalii bromidum; 2. agents obtained from plants: Valeriana, Leonurus, Passiflora, Peony, etc.; 3. combined drugs: bromated camphor, corvalolum, barbovalum, cardiovalenum, novo-passit, persen, and sanason.

The action of bromides depends on the type of nervous system: in the case of a "weak" type the action is increased and a dose should be lower than the ordinary one and in a "strong" type — on the contrary. That is why the doses of bromides have to

be determined individually. The bromides are excreted from the organism rather slowly (50-60 days), so they may be accumulated and cause the signs of chronic poisoning (bromism) which is manifested in weakness, sleepiness, apathy, decrease of memory, and acneiform eruption on the skin (bromide acne). The irritative action of bromides leads to inflammation of the mucous membranes, which is accompanied by cough, rhinitis, conjunctivitis, and diarrhea. The treatment of bromism is carried out by interrupting to take bromides and speeding up their excretion. The excretion of bromides with the urine may be increased by indication of high amounts of sodium chloride, water, and diuretics.

The agents derived from plants (Valeriana, Leonurus, Passiflora, peony, etc.) contain different ethereal oils, alkaloids, organic acids, or other substances which exert calmative action. They are well endured by patients and do not cause side-effects and drug dependence.

Antidepressant agents

Depression is an alteration of mood characterized by sadness, worry, and anxiety.

The **amine hypothesis of mood** postulates that brain amines, particularly noradrenaline (NE) and serotonin (5-HT), are neurotransmitters in pathways that function in the expression of mood. According to the amine hypothesis a functional decrease in the activity of such amines would result in depression; increase of activity would result in mood elevation. Most antidepressants are believed to improve mood by increasing catecholamine stores, although recent evidence suggests that there may be a correlation between improvement in mood and a decrease in adenylate cyclase.

The major classes of antidepressant drugs are: nonselective catecholamine reuptake inhibitors (**tricyclic antidepressants, heterocyclic antidepressants**), **selective serotonin reuptake inhibitors**, and **monoamine oxidase inhibitors**.

Nonselective catecholamine reuptake inhibitors. Tricyclics (TCAs): tricyclic antidepressant drugs, e.g. **imizinum (imipraminum), amitriptylinum** are structurally related to the phenothiazine antipsychotics and share certain of their pharmacologic effects. **Heterocyclics** have varied structures and include second-generation antidepressants (e.g. **pyrazidolum, maprotilinum, trazodonum**) and newer, third generation drugs (**mirtazapinum, venlafaxinum**). **Selective serotonin**

reuptake inhibitors (SSRIs) are **fluoxetine, fluvoxanin, sertraline, citalopram, paroxetine** are the prototype of a group of drugs which selectively inhibit the reuptake of serotonin. The **MAO inhibitors (MAOIs)**, e.g. **nonselective nialamidum, selective pyrazidolum**, and **moclobemidum** are structurally related to amphetamines and are orally active.

Pharmacokinetics: The **tricyclic antidepressants** are well absorbed from the gastrointestinal tract. Because of their lipophilic nature, these agents become widely distributed and have relatively long half-lives. They are metabolized in the microsomal metabolizing system. Hydroxylation, N-demethylation, and conjugation with glucuronic acid are the major metabolic pathways. The demethylated metabolites of both amitriptyline and imipramine have antidepressant activity. Excretion of metabolites is via the kidney. **Selective inhibitors of serotonin** are well absorbed after oral ingestion. They undergo extensive hepatic biotransformation: some metabolites are active; metabolites are excreted in the urine. The onset of action is within 1-3 weeks after the treatment.

Pharmacologic and CNS effects. **Tricyclic antidepressants** have both antihistaminic (H_1 -receptor-blocking) and α -adrenergic properties. The tricyclic antidepressants possess antimuscarinic action and block the reuptake of serotonin. Tertiary amines (imipramine, amitriptyline) are more effective at blocking serotonin uptake. A nondepressed person experiences sleepiness when a tricyclic antidepressant is administered. In addition, anxiety and toxic anticholinergic effects may be experienced. Amitriptyline has prominent sedative effect. In a depressed patient, an elevation of mood occurs 2-3 weeks after administration begins. The latency period can be as long as 4 weeks. Tricyclic antidepressants may cause extrapyramidal symptoms and ataxia. High doses of tricyclic antidepressants are capable of producing seizures and coma. **Cardiovascular effects:** Orthostatic hypotension and arrhythmias are two common effects. Tachycardia may occur in response to the hypotension and interference with atrioventricular conduction similar to that produced by quinidine. The most common autonomic **nervous** system effect is anticholinergic. Amitriptyline possesses the most potent antimuscarinic effects.

Amitriptylinum is thought to be better tolerated than imizinum in older psychotic or depressed patients. Amitriptylinum is effective in multiple sclerosis patients with **pseudobulbar palsy**, the syndrome of pathologic laughing and weeping. **Desipraminum**, the monodesmethyl derivative of imizinum, is less sedating than its parent compound. **Clomipraminum**, like desipramine, produces less sedation than its parent compound amitriptyline. **Doxepinum** is also effective in treating depression when anxiety is present. **Maprotylinum** differs by its structure and causes little sedation.

Fluoxetine (prozak), fluvoxaminum (fevarinum), sertralinum (Zoloft), citalopramum (cipramilum), paroxetinum (paxilum), escitalopramum (cipralezum) **are selective inhibitors** of serotonin uptake in the CNS. They have little effect on central noradrenaline or dopamine function, less adverse effects because of minimal binding to cholinergic, histaminic, and α -adrenergic receptors.

The **MAO inhibitors** increase noradrenaline in sympathetic nerve terminals. This can lead to peripheral autonomic sympathomimetic effects. Long-term use of the MAOIs can decrease blood pressure. Sedation is a common CNS effect of tricyclic drugs (although it is less with imizinum and with most heterocyclic agents). The MAO inhibitors, selective serotonin reuptake inhibitors are more likely to cause CNS-stimulating effects. The increase of biogenic amine levels in the brain is thought to underlie the observed antidepressant effects. There are two types of the MAO inhibitors: nonselective - nialamidum which influences the MAO-A and MAO-B and selective – pyrazidolum and moclobemidum which influence only the MAO-A. Besides their effect on depression the MAO inhibitors are effective in sleep disorders, including narcolepsy. They suppress fast sleep. Except for nialamidum, which has a stimulant effect, other MAO inhibitors have minimal psychostimulant effect.

Cardiovascular effects: Hypotension, especially postural, can result from administration of the MAO inhibitors to affect ganglionic transmission and reduce the release of norepinephrine in certain organ systems. This effect is believed to be due to the uptake and release of "false transmitters," such as tyramine. The MAO inhibitors can **interact with foods containing a high tyramine content, such** as cheese, beer,

and chicken liver. High concentrations of tyramine absorbed from these foods cannot undergo oxidative deamination. This can precipitate a **hypertensive crisis**, which is the most serious adverse effect which is caused by MAO inhibitors.

Hepatic effects: The MAO inhibitors interfere with the detoxification of many drugs.

Therapeutic uses: Tricyclic antidepressants are considered the treatment of choice for severe endogenous depression (characterized by regression and inactivity). In terms of overall efficacy various tricyclic antidepressants are equivalent at appropriate dosages. Enuresis has been successfully treated with imipramine. Obsessive and compulsive neurosis accompanied by depression, and phobic and anxiety syndromes, chronic pain, and neuralgia may respond to tricyclic agents.

Antidepressants which are selective blocking uptake of serotonin are used for treatment of endogenous depression. They are useful in treating obsessive and compulsive disorder, obesity, and alcoholism.

The **MAO-A inhibitors** (pirazidolum and moclobemidum) are especially effective in the treatment of atypical depression, characterized by symptoms such as hypersomnolence, hyperphagia, and hyperanxiety.

Adverse effects: Anticholinergic effects of tricyclic antidepressants can be prominent and occur both peripherally and centrally. Amitriptyline produces the highest incidence of antimuscarinic effects. Tolerance often develops to these effects. Sweating is common. The elderly may suffer from dizziness and muscle tremor. Cardiac arrhythmias can occur. Hypotension is frequent and results from a down-regulation of adrenergic receptors. Manic excitement and delirium can occur in patients with bipolar illness. Less common adverse effects include skin rashes, cholestatic jaundice, and orgasmic impotence. Acute poisoning is often treated with activated charcoal, although gastric lavage and physostigmine have been used successfully as adjuncts. Vital functions need to be supported and constantly monitored, since seizures, ventricular arrhythmias, and death can result from overdoses. The combination of a MAO inhibitor with a tricyclic antidepressant should be avoided, since hyperpyrexia, convulsions, and coma may occur.

Second-generation antidepressants differ from the previous agents primarily in terms of their more favorable side-effect profiles. Specific agents include **tertiary compound, maprotilinum etc.** These drugs have few anticholinergic effects.

The selective drugs cause anorexia and, unlike the tricyclics, do not cause weight gain. They may precipitate mania or hypomania. Nausea, nervousness, headache, and insomnia occur more frequently than with tricyclics. Urticaria or some other rash develops very seldom.

The most serious effect of this drug is marked hypertension from an interaction between a MAO-A inhibitor and certain amines or their precursors. Nialamidum can cause hepatocellular damage. Excessive CNS stimulation may occur, resulting in insomnia and convulsions. Nialamidum overdosage may result in agitation, headache, hallucinations, convulsions, and hypotension or hypertension.

№	Drug	Drug forms
1.	Imizinum	Tab. 0,025; Amp. 1,25 – 2ml
2.	Amitryptilinum	Tab. 0,025; Amp.1% - 2ml
3.	Sertralinum	Tab. 0,025, 0,05, 0,1
4.	Fluoxetinum	Caps. 0,02
5.	Fluvoxaminum	Tab. 0,1
6.	Nialamidum	Tab. 0,025
7.	Pyrazidolum	Tab. 0,025, 0,05

CNS STIMULANTS

Drugs which stimulate the CNS are called psychotropic drugs with exciting type of action. Some of them improve memory, integrative action of mind, reflex, and activity.

Classification of psychostimulators:

1. Psychomotor stimulators;
2. Nootrope drugs;
3. Actoprotectors;
4. Adaptogens;
5. Antidepressants;
6. Analeptics.

Psychomotor stimulators are divided into:

1. Derivatives of purine: Coffeinum-natrii benzoas;
2. Derivatives of fenilalkylamines: Phenaminum (amphetamine), Sydnocarbum;
3. Derivatives of piperidine: Meridinum.

Derivatives of Phenylalkylamines

Mechanism of action: These drugs release catecholamines from deposits, inhibit catecholamines reuptake, MAO activity and increase receptors sensitivity to catecholamines

Psychostimulators (Amphetamine, Phenaminum, Sydnocarbum)

In addition to its peripheral sympathomimetic action, phenaminum is a powerful CNS stimulant. Phenaminum stimulates a medullary respiratory centre and has analeptic **action**, counteracting the central depression produced by other drugs (e.g. barbiturates). Phenaminum increases alertness, decreases sense of fatigue, increases motor and speech activity, and elevation of mood is often achieved. Phenaminum has anorectic effect. It may cause hypnosis after excitation and has drug dependence. Phenaminum is not used because of drug dependence.

Adverse effects: Dysphoria, headache, confusion, dizziness, fatigue, or delirium may be observed. Blood pressure is usually raised, and cardiac arrhythmias

may occur. Larger doses or prolonged usage are usually followed by fatigue and mental depression.

Sydnocarbum acts similar to phenaminum but does not cause drug dependence, hypnosis, less influences on peripheral adgenoreceptors. It is used in the case of neurotic disorders, asthenia, braking, apathy, sleepiness, decrease of mood and capacity for work, alcoholism with braking, lifeless schizophrenia.

Adverse effects are the following: restless, irritation moderate increase of blood pressure decrease of appetite.

The derivative of pyrimidine – **meridilum** is less active than sydnocarbum. It does not cause drug dependence and peripheral adrenomimetic effects. It is seldom used.

A typical derivative of purine or xanthine is **coffeinum-natrii benzoas**. Coffeinus is alkaloid of leaves of *Thea sinenses*, semens of *Coffea arabica*, *Cola acuminata*, and other plants.

Pharmacokinetics: Coffeinum is well absorbed from the gastrointestinal tract as water solving salts. Coffeinum is metabolized in the liver by means of dimethilation and oxydation into inactive metabolites. 10% of a given dose is excreted in the urine, faeces as an unchanged drug. The drug completely eliminates within 24 hours.

The mechanism of Coffeinum action is antagonism with adenosine for adenosine receptors; or antagonism of the presynaptic inhibitory effects of adenosine inhibition of enzyme phosphodiesterase which leads to accumulation of cAMP, release of calcium from sarcoplasmium reticulum. Coffeinum can compete for binding at the benzodiazepine site and would be expected to reduce chloride conductance.

Pharmacological effects: Coffeinum causes excitation in the cerebral cortex, increases mood and capacity for work, relieves perception, speeds the time of reaction, decreases sleepiness, exhaustion. Coffeinum excites respiratorum vascular moving, vagus centres of medulla oblongata, increases of excitation of medulla spinalis. The effect of coffeinum is more expressive during exhaustion. Coffeinum

has positive inotropic and chronotropic actions which are more expressed in the case of weakness and myocardium. Pulse breathing may be stimulated, oppressed, not changed because of different influences. Coffeinum widens the vessels of heart, kidney, lungs, skeletal muscles, narrows abdominal capacity. It widens the vessels of brain first and then narrows them. Coffeinum increases gastric glands secretion, main metabolism, diuresis.

Therapeutic uses: It decreases the mood and capacity to work, sleepiness, exhaustion. It is used to treat migraine, arterial hypotension. It is a component of tablets with acidum acetylsalicylicum in the treatment of headache, and with an ergot derivative - to treat migraine.

Adverse effects are: nausea, vomiting, worry, insomnia, cardiac arrhythmia. During long administration of coffeinum it may lead to tolerance and drug psychotic dependence (theisms).

Adaptogenes

Adaptogenes are the drugs mainly of plant origin which have commonly tonicising influence on the main functions and systems, they increase stability of organism to unfavourable factors. The representatives of adaptogens are **tincturae and liquid extracts of Schizandrae, Ginsengi, Rodiolae, Eleutherococci, Leuzeae, Echinaceae, Echinapanacis**. There are also drugs – **pantocrinum** and **saparalum** which are derived from antlers.

Mechanism of adaptogenes action is connected with activation of nucleonic, protein metabolism, oxidative phosphorylation, and normalizing of function of hypophysis – adrenal and immune systems.

Pharmacologic effects: They increase mood and capacity to work, stability of organism to unfavourable factors, the specific and nonspecific immunity, improve blood circulation, haemopoiesis, breathing, vision, and hearing. They have cardioprotective and hepatoprotective effects.

Therapeutic uses: They are used to treat physical and mood overstrained, asthenia syndrome, status after inflectional and somatic diseases, and influence of radiation.

Adverse effects may be: excitation of nervous and cardiovascular system, arterial hypertension, and hyperglycemia.

Actoprotectors

Actoprotectors are the stimulators of capacity to work, which increase the stability of organism to oxygen starvation and high temperature. Bemethylum is a derivative of benzimidazolium. It has an antihypoxic and psychostimulating action. It increases the stability of organism to physical overloads.

Mechanism of action of Bemethylum is connected with stimulation of adenyl nucleotides synthesis, decrease of exhaustion processes and necessity in oxygen.

Therapeutic uses in cases of : asthenia status, neurosis, status after traumas, infection diseases.

Adverse effects are the following: nausea, seldom, vomiting, unpleasant feeling in stomach, headache, and hyperemia of face skin.

Vitamins metabolic drugs (phosphokreatinum, ATP-long, mexidolum etc.) have also actoprotector activity.

Nootropic drugs

Nootropic agents are drugs which favourably influence metabolism, improve psychic, mood activity in the cases of pathologic status. There are following major groups of nootropic drugs:

1. Derivatives of pyrrolidones (racetanes) – Piracetamum-nootropil, etiracetamum, pramiracetamum etc.;
2. Derivatives of the GABA – Aminoaloonum, Natrii oxybutyras, Phenibutum, Pantogamum, Picamilonum etc.;
3. Neuropeptides and its analogues – Synacten-depot, Thyroliberinum etc.;
4. Cerebrovascular drugs – Nicergolinum-Sermionum, Vinpocetinum-Cavintonum, Pentoxifyllinum-Trentalum, Agapurinum, Xantinoli nicotinas, Complaminum, Nimodipinum-Nimotapum, Cinnarizinum-Stugeronum etc.;
5. Derivatives of Pyridoxinum (Pyritinolum-encephabolum etc.);
6. Antioxydants – Tocopheroli acetat, Acidum nicotinicum, Mexidolum, Berlithionum, Melatoninum etc.;

7. Drugs of other groups – anticholinesterase drugs (galanthamini hydrobromidum, rovastigminum), M-cholinomimetic, derivative of amino-acides-glycine (glycesedum, noopeptum), acidum glutaminicum, citicolinum, and other synthetic drugs and hydrolysate of blood - naphthhydrofurilum, enalbinum, cerebrolysinum, cerebrocurinum, actoveginum, solcoserilum etc., plant drugs - tanacatum, memoplantun etc.

The main drug is **pyracetamum** — a cyclic compound of the GABA.

Pharmacokinetics: Pyracetamum is quickly absorbed from the gastrointestinal tracts. It distributes in many systems and organs and penetrates through haematoencephalic and placentic barriers. Pyracetamum is accumulated in cerebral tissues. 90 % of drug is excreted without changing in the urine.

Pharmacologic effects: Pyracetamum improves memory, mental faculties and other integrative processes. It improves comprehension of glucose metabolism of the ATP, phosphatidinetanol, and phosphatidilcholine, increases activity of adenylatcyclase, phosphalipase A₂, stability of tissues to oxygen insufficiency, oppresses activity of nucleotide phosphatase. It stimulates RNA synthesis and circulation in cerebral tissues. It has antioxidant influence; cardioprotective and anticonvulsant action.

Therapeutic uses: It is used in cases of decrease of mental functions in elderly patients after traumas, blood-stroke, psychic diseases, alcoholism and other abstinent syndromes, mental insufficiency in children.

Adverse effect may be as follow: tremor, insomnia, irritation, and dyspepsia.

Aminalonum differs from pyracetamum because it badly penetrates through haematoencephalic barrier, may cause bradycardia, hypotension, has more anticonvulsant action. **Vinpocetinum** is alkaloid of Vinca minor, which improves cerebral and peripheral circulation of blood and metabolism. **Nicergolinum**, α_1 -adrenoblocker, improves cerebral circulation of blood and metabolism, decreases arterial pressure. **Pentoxifyllinum** improves cerebral, peripheral circulation of blood, metabolism, rheological properties of blood, has antianginal, hypertensive, and immunomodulative action.

Therapeutic uses of these drugs are similar to pyracetamum.

Analeptics

The analeptics are the stimulators of the CNS of common action.

The analeptics are divided according to localization of their action in the CNS:

1. Drugs which influence cerebrum: Coffeini-natrii benzoas;
2. Drugs which influence medulla oblongata: Aethimizolum, Cordiaminum, Camphora, Sulfocamphocainum, Bemegridum (??? not used in Ukraine), Carbogenum;
3. Drugs which influence medulla spinalis: Strychnini nitras.

The analeptics are divided according to the types of action:

1. Analeptics of direct action: Coffeinum-natrii benzoas, Aethimizolum, Bemegridum;
2. Analeptics of reflexive action: Lobelini hydrochloride, Cytitonum, Sol. Ammonii castici;
- 3) Analeptics of mixed action: Cordiaminum, Carbogenum, Camphora, Sulphocamphocainum.

Bemegridum is seldom used in some countries. In case of overdosing narcotic and hypnotic drugs, it more influences on respiratory centre.

Cordiaminum exercises influence on respiratory and vascular and moving centers, increases arterial pressure, circulation amplitude of breathing, improves metabolism of heart, extitates spinal cord. It has hepatoprotective properties as a derivative from acidum isonicotinicum and antipellagic. Cordiaminum is used in the conditions of weakness of breathing during inflectional diseases, asphyxia, a shock during surgical operations and narcosis.

Adverse effects may be the following: clonic convulsions, face hyperemia, pain in case of subcutaneous and intramuscular injections. **Camphora** has local antimicrobial, and irritative action. Resorbtive action of Camphora is displayed in stimulating influence on respiratory and vascular moving centres, heart, increasing blood circulation, synthesis of interferon. Camphora has expectorative influence.

Therapeutic uses are: acute and chronic cardiac insufficiency, oppression of

breathing in pneumonia and other inflectional diseases, intoxication of narcotics and hypnotic drugs. **Sulphocamphocainum** is more soluble in water than camphora because novocainum is a component of this drug. It is administered subcutaneously, intravenously, and intramuscularly. **Carbogen, aethimizolum** (see drugs which influence the system of breathing), cytitonum, lobelini hydrochloride (see N-cholinomimetic drugs), Sol. Ammonii causticum (see irritative drugs). **Strychnini nitras** – is an alkaloid of *Strychnos nux vomica*. Strychnini nitras influences centers of spinal cord, competes with glycine for receptors, increases the tonus of skeletal muscles, functions of visional and acoustic analyzers, influences centers of medulla oblongata.

Therapeutical use for seldom diagnostics of visional analyzer.

Adverse effect might be: tetanic convulsions, difficulty of breathing, and swallowing.

№	Drug	Drug forms
1.	Coffeinum-Natrii Benzoas	Tab. 0,1, 0,2; Amp. 10%, 20% - 1, 2ml
2.	Sydnocarbium	Tab. 0,005, 0,01, 0,025
3.	Pyracetamum	Caps. 0,4; Tab. 0,2, 0,8; Amp. 20% - 5ml
4.	Pentoxifyllinum (Trental)	Tab. 0,1, 0,4, 0,6; Dragee 0,1 Amp. 2% - 5ml
5.	Vinpocetinum	Tab. 0,015 Amp. 0,5% - 2ml
6.	Nicergolinum	Tab. 0,01
7.	Tinctura Ginseng	Flac. 50ml
8.	Extr. Eleutherococci	Flac. 50

	Fluidum	
9.	Extr. Leuzeae Fluidum	Flac. 40ml
10.	Tinctura Schizandrae	50ml
11.	Pantocrinum	30, 50ml; Tab. 0,075; 0,15; Amp. 1, 2ml
12.	Cordiaminum	Amp. 1, 2ml; 15ml
13.	Sulfocamphocainum	Amp. 10% - 1ml
14.	Aethimizolum	Pulv.; Tab. 0,1; Amp. 1%, 1,5% - 3, 5ml

Drugs affecting the respiratory system.

Drugs affecting the respiratory system are divided into 5 groups:

1. Respiratory stimulants;
2. Drugs used to treat cough (Antitussives);
3. Expectorants;
4. Bronchodilators (drugs used to treat asthma);
5. Drugs used to control pulmonary edema.

Respiratory stimulants

Respiratory stimulants are classified according to corresponding influence on the sides of the CNS and by type mechanism of action. Frequency and depth of breathing are regulated by breathing center. Respiratory stimulants excite breathing centre and than increase lung ventilation and gas metabolism, oxygen content and decrease carbonic acid level. They increase metabolism products excretion, stimulate oxidative processes and acid-based equilibrium. They may increase arterial pressure by excitation of vessel moving centre and increase of haemodinamics.

The respiratory stimulants may be divided:

1. Drugs which mainly influence cortex (coffeinum-natrii benzoas);
2. Drugs which mainly influence medulla oblongata (Aethimizolum, Camphora,

Sulfocamphocainum, Cordiaminum, Bemegridum);

3. Drugs which mainly influence spinal cord (Strychnini nitras).

They are also divided into:

1. Drugs of direct action on respiratory centre (Coffeini natrii benzoas, Aethimizolum, Bemegridum);

2. Drugs of reflexive action (Lobelini Hydrochloride, Cytitonum, solutio Ammonii causticum);

3. Drugs of mixed action (Carbogenum (95-93 % O₂, 5-7 % CO₂), Cordiaminum, Camphora, Sulfocamphocainum).

Bemegridum is not used in Ukraine.

Aethimizolum is a derivative of dicarbone acid, blocks phosphodiesterase accumulates cAMP, increases frequency and depth of respiration, heart rate, dilutes bronchial muscles. It may stimulate formation of glucocorticoids, has antinflammatory immunomodulative action, increases tonus of cardiac and skeletal muscles. The drug has a sedative action. It is used in overdosage or poisoning with narcotic drugs for general anesthesia, alcohol, hypnotic drugs, in the case of asphyxia of newborns.

Adverse effects may be the following: dyspepsia, disturbance of sleep, anxiety, dizziness.

Camphora is terpene ketone from silver fir oil which is half synthetic. **Sulfocamphocainum** is a derivative of sulfocamphoral acid and Novocain and may be administered intravenously, subcutaneously, intramuscularly. These drugs stimulate respiratory and cardiomotor centres. Camphora stimulates heart. Camphora and sulfocamphocainum are used in cases of poisoning by narcotic drugs, carbonate oxydum in asphyxia, cardiac insufficiency.

Adverse effects. Camphora may cause irritation and sulfocamphocainum –idiosyncrasy.

Cytitonum, and **lobelini hydrochloride** stimulate N-cholinoreceptors located in the CNS, carotide glomerules, and adrenal medulla. They are used as respiratory stimulants very seldom, more often in case of poisoning with carbonate oxide.

Solutio Ammonii causticum irritates receptors of nose mucosa and then respiratory centre in case of dizziness by reflex.

Carbogen excites vasomotor centre, narrows peripheral vessels. It is used in case of poisoning by narcotic agents, carbonic oxide, asphyxia, different diseases with insufficiency of

respiratory system.

Antitussines

Antitussines are divided into:

1. Drugs of central action:

a) Opioides – codeine phosphus, aethylmorphini hydrochloridus which suppress the cough reflex by depressing a medullary cough centre;

b) Nonopioide drugs – glaucini hydrochloride, oxeladini cytras, and synecodum.

2. Drugs of peripheral action:

Libexinum which has broncholytical and local anesthetic effect.

Falimint has also antimicrobial effect. The antitussives are used in case of dry cough.

Expectorants

These drugs are divided into:

1. Bronchosecretor drugs which assist liquid mucose expelling;

2. Mucolytics which melt mucose.

Bronchosecretor drugs are classified as:

a) Drugs of reflector action - infusum herbal Thermopsidis, decoctum radidis Althaeae, Mucaltinum;

They irritate receptor of stomach mucosa, increase secretion of bronchial glands, contractility of epithelium and muscles and help mucus expelling. Infusum herbae Thermopsidis also excites respiratory centre. Decoctum radidis Althaeae and Mucaltinum have covering effect.

b) Resorbitive action;

Kalii iodidum which excretes through glands, melts mucus and stimulates secretion. Natrii hydrocarbonate changes pH to base district and stimulates secretion.

3. There are mixed expectorants.

Mucolytics are divided into:

a) proteolytic enzymes;

They tear peptide connections, change physicochemical properties of mucus. There are such drugs as Trypsini crystallisatum, Chymotrypsin crystallisatum, Desoxyribonucleasa, Ribonucleasa. Two last drugs change depolimerisation of nucleonic acids

b) Synthetic mucolytics – Acetylcysteinum, Carbocysteinum;

They have sulfhydryl groups that tear disulfide connections and help mucus expelling. Besides this acetylcysteine is antioxidant, cardioprotector, antidote of paracetamol.

c) Synthetic mucolytics that increase synthesis of surfactant – Bromhexin, Ambroxol;

These drugs also have thiogroups which open mucoproteins disulfide groups, reducing the viscosity of mucus. They will not provoke bronchospasm in patients with bronchial asthma.

d) Drugs of surfactant which change surfactant content in alveoli – Alveofact, Exosurf.

Bronchodilators

Airflow obstruction in asthma is due to the inflammation of bronchial wall, contraction of bronchial smooth muscle, increased mucus secretion causing shortness of breath and makes respiration difficult. An asthmatic attack may be precipitated by inhalation of allergens (dust, perfume, pollen, animal) which interact with mast cells coated with immunoglobulin E, generated in response to a previous exposure to allergen. The mast cells release mediators such as histamine, leukotrienes, and hemotoxic factors, which promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Many asthmatic attacks are not related to a recent exposure to allergen, but rather reflect bronchial hyperactivity of unknown origin which is somehow related to inflammation of the airway mucosa. The symptoms of asthma may be effectively treated by several drugs, but no one of the agents provide a cure for this obstructive lung disease.

There are five groups of the bronchodilators:

1. Adrenergic agents;

The adrenergic agents with beta activity are the drugs of choice for mild intermittent asthma. These potent bronchodilators relax airway smooth muscle and inhibit the release of substances from mast cells which cause bronchoconstriction. The most common agents are beta₂-adrenomimetics – salbutamol, fenoterol, terbutalin, formoterol, salmeterol, and clenbuterol. Salbutamol, fenoterol, terbutalin are the drugs of short duration (4-5 hours) and are used for prevention and treatment of asthma attacks. Salmeterol, clenbuterol, and formoterol have a prolonged action and are used for prevention of asthma attacks.

Beta_{1,2}-adrenomimetics (isadrin and orciprenaline sulfates) are used seldom. In acute attack

adrenalini hydrochloridum and ephedrini hydrochloridum may be administered.

Stimulation of beta₂-adrenoreceptors leads to increasing of cAMP – concentration, decreasing of Ca²⁺ ion concentration, relaxation, stabilization of basophilic cell, and membranoprotection action.

2. M-cholinoblockers are less effective-Ipratropii bromidum, Atropini sulfas, Platyphyllini hydrotartras, Methacinum are used as bronchodilators. They increase cGMP concentration, decrease Ca²⁺ ions concentration lead to smooth muscle relaxation. Inhaled ipratropii bromidum a quaternary derivative of atropine sulfas is useful in patients unable to take adrenergic agonists.

3. Myotropic broncholytics (Xantines).

When asthmatic symptoms cannot be controlled with adrenergic agents addition of the methylxanthine derivatives may be appropriate. Myotropic bronchodilators relieve airflow obstruction in acute asthma and decrease the symptoms of chronic diseases. The drugs are well absorbed in gastrointestinal tract and there are several sustained release preparations. There are ephyllinum, theophyllum in that group. Overdoses of the drugs may cause seizures or arrhythmias.

4. Nonsteroid inflammatory drugs.

Cromolyn–sodium is an effective prophylactic agent which stabilizes the membrane of most cells and prevents mediator release by blocking calcium gate. The drug is not useful in managing in acute asthmatic attack. For use in asthma cromolyn-sodium is administered as inhalation of a microfine powder or as an aerosolized solution. Because it is poorly absorbed only minor adverse effects are associated with it. Pretreatment with cromolyn–sodium blocks allergen-induced and exercise–induced bronchoconstriction. Cromolyn–sodium is also useful in reducing the symptoms of allergic rhinitis. Not all patients respond to a cromolyn–sodium therapy, but those who do respond to the treatment show improvement which is roughly equal to the improvement obtained from main tename ephyllum or theophyllum therapy. Nedochromylum–natrium is more effective. It also decreases content of leucotriens and stimulates neuropetide C.

Ketotiphenum decreases histamine release and blocks H₁-histamine receptors. It is used for prophylactic of bronchospasm. It is possible to use other antihistaminic drugs (diprazinum, suprastinum and others).

5. Corticosteroids .

Prednisolonum, dexamethasonum, triamcinolonum, budesonidum, flunisolidum, fluticasonum, and beclomethasonum are used for prevention of bronchial asthma attacks.

Drugs used to control pulmonary edema:

I. Drugs decreasing hydrostatic pressure in lung vessels.

1. Natrii nitroprussidum and organic nitrates (nitroglycerinum, isosorbidi dinitras);
2. Ganlioblockers (pentaminum, benzohexonium, hygronium);
3. Broncholytics (euphyllinum);
4. Drugs with alpha – blocking properties (aminazinum, diprazinum);
5. Tranquilisers (diazepamum);
6. Opioid analgetics (morphini hydrochloridum);
7. Narcotic analgetics with neuroleptics (phentanylum + droperidolum or haloperidolum);
8. Corticosteroids (prednisolonum and others).

II. Drugs improving heart contractility.

1. Cardiac glycosides (corglyconum, digoxinum, strophanthinum);
2. Nonglycosides cardiotonics (dophaminum, dobutaminum), may be administered with the APE inhibitors;

III. Drugs decreasing circulating blood volume.

1. Loop diuretics – furosemidum, torasemidum.
2. Osmotic diuretics in the conditions of tolerancy to furosemidum (mannitolum, mannitum, urea pura rarely)

IV. Drugs restoring normal bronchial and bronchiols passage transforming gas into alveols in liquid (alcohol).

Nº	Drug	Drug forms
1.	Aethimizolum	Pulv., tab. 0,1; Amp. 1%, 1,5% - 3, 5ml
2.	Libexinum	Tab. 0,1
3.	Oxeladini citras	Tab. 0,01, 0,02 Sirupus 100ml

- | | | |
|-----|--|---|
| 4. | Ambroxolum
(Lasolvan) | Tab. 0,03;
Caps. 0,075;
Sirupus 100ml (5ml – 0,015);
Supp. rect. 0,015;
Amp. 0,75 – 2ml;
Flac. 100ml (1ml – 0,075) |
| 5. | Bromhexinum | Tab. 0,008 |
| 6. | Acetylcysteinum | Amp. 10% - 2ml
20% - 5,10ml;
Tab. 0,1, 0,2 |
| 7. | Trypsinum
crystallisatum | Amp., flac. 0,05, 0,1 |
| 8. | Infusum herbae
Thermopsidis | Ex 0,6 – 180ml |
| 9. | Infusum Radicis
Althaeae | 1:30
1:10 |
| 10. | Mucaltinum | Tab. 0,05 |
| 11. | Fenoteroli
hydrobromidum
(Berotec) | Flac. 15ml (0,0001 – 0,0002 pro
dosis) |
| 12. | Ipratropii
bromidum
(Atrovent) | Flac. 15ml (0,0002 pro dosis) |
| 13. | Euphyllinum | Pulv.;
Tab. 0,15;
Amp. 2,4% - 10ml;
Amp. 24% - 1ml |

Cardiovascular Agents

Drugs which influence cardiovascular system are divided into:

1. Drugs which influence heart function:

- 1.1 Cardiotonic drugs;
- 1.2 Antiarrhythmic drugs;
- 1.3 Antianginal drugs.
2. Drugs which are used in conditions of violation of vessels function:
 - 2.1 Antihypertensive drugs;
 - 2.2 Hypertensive drugs;
 - 2.3 Angioprotectors;
 - 2.4 Drugs which improve microcirculation;
 - 2.5 Drugs that influence on the cerebral blood circulation.

DRUGS USED IN THE TREATMENT OF CONGESTIVE HEART FAILURE

Drugs which are used in cardiac heart failure, increase or normalize heart contractility are called direct and indirect cardiotonic drugs.

Direct cardiotonic drugs are those which influence the function and metabolism of myocardium. They are divided into:

1. Steroid cardiotonic drugs (cardiac glycosides);
2. Nonsteroid cardiotonic drugs (dopaminum, dobutaminum, amrinonum, milrinonum, lavasimendanum etc).

Indirect cardiotonic drugs include antihypertensive, antianginal, diuretic drugs which relieve cardiac contraction, decrease pre- and postload on myocardium.

There are such groups of indirect cardiotonic drugs:

1. The ACE inhibitors (captoprilum, enalaprilum etc);
2. Diuretics (antagonists of aldosterone — spironolactonum, eplerenonum, loop diuretics — furosemidum, torasemidum, acidum etacrxinicum, sometimes thiazide and thiazidelike diuretics);
3. β -adrenoblockers — metoprololum, bisoprololum; α - β -adrenoblockers: carvedilolum etc.;
4. Antagonists of angiotensin receptors: losartanum, telmisartranum etc.;
5. Calcium channel-blockers drugs: amlodipinum;
6. Sometimes α -adrenoblockers: prazosinum, doxazosinum (without

provments).

There are new groups of cardiotoxic drugs:

1. There are data about efficiency of neutral endopeptidase blockers – candoxatrilum etc.;
2. Complex ACE inhibitors and neutral endopeptidase blockers: omapatrilatum etc.;
3. Endotheline antagonists: bosentanum etc.;
4. Cytokine antagonists: pentoxyphyllinum etc.;
5. Drugs with complex mechanism: drug of natriuretic peptide-neseretidum, vesnarinonum etc.

Antihypertensive drugs decrease systolic arterial pressure, promote more perfect emptiness of left ventricular in systole, increase its fullness in early diastolic phase, cause reverse development of left ventricular hypertrophy.

Antianginal drugs (vasodilators of organic nitrates) β -adrenoblockers, calcium channel blockers improve diastolic function of left ventricular when it disturbs and connects with ischemia of myocardium. Diuretics and vasodilators decrease preload, pressure in right ventricular and indirectly in left ventricular. ACE inhibitors decrease vasoconstrictors level (angiotensin II, endotheline, vasopressin, aldosterone, catecholamines), increase vasodilators level (bradikininum, nitrogenum oxide), delay progress of cardiac insufficiency, decrease lethality, increase duration of life. β -adrenoblockers in the conditions of cardiac insufficiency have different neurohumoral mechanisms.

1. Breaking of adverse effects of neurohumoral regulation;
2. Decrease applies of energy and increase of cardiac function by means of decrease of cardiac contractions frequency;
3. Decrease of oxygen applies;
4. Increase of parasympathic tonus and prevention of arrhythmias including ventricular fibrillations;
5. Cardioprotection.

CARDIAC GLYCOSIDES

Cardiac glycosides are complex compounds of plant origin which do not consist of nitrogen and have selective cardiotonic effect. There are half-synthetic glycosides – metylazidum, acetyldigoxinum, strophanthidini acetat etc. Curative properties of cardiac glycosides have been determined in 1785 by the English doctor W. Withering. Toxicologist E.V. Pelickan (St. Petersburg) studied strophanthinum influence on a frog heart. S.D. Botkin, therapist (Moscow) elaborated schemes of digitalis drugs prescriptions and organized a laboratory for investigation of cardiac glycosides action. Physiologist I.P. Pavlov (St. Petersburg, Moscow) studied cardiac glycosides action on the CNS. N.D. Strazhesko (Kiev) established the principle of intravenous strophanthine administration. A.I. Cherkas determined a trophic action of cardiac glycosides in 1949.

There is a classification of cardiac glycosides according to their origin:

I. Digitalis drugs.

1.1. Digitalis purpurea drugs – digitoxinum (cardiotoxinum, digiphonum, and cardiginum);

1.2. Digitalis (lanata) – digoxinum (dilanacinum, lanicor, lanoxinum), celanidum (isolanidum, lanatosidum C), medilasidum (bemecor, lanitop), lantosidum.

II. Strophanthus drugs.

2.1. Strophanthus Kombe – strophanthinum K;

2.2. Strophanthus gratus – strophanthinum G (oubaine).

III. Convallariae drugs: Corglyconum, Tinctura Convallariae.

IV. Adonis vernalis drugs: Infusum herbae Adonidis vernalis, adonisidum, cardiophytum, cardiotonum.

V. Erysimum drugs – cardiovalenum.

Cardiac glycosides are the combination of an aglycone or genin, and glycone.. **The aglycone** consists of steroid and lactone rings. It is a pharmacologically active portion of the glycosides. Aglycone is connected with pharmacodynamics. The glycone (sugars) modify the water- and lipid-solubility of the glycoside molecule and, thus, affect their potency and duration of action. The sugars are specific (digitoxosum) and nonspecific (glucosum). Glycone is connected with

pharmacokinetics.

The term **digitalis** is frequently used to refer to the entire group of cardiac glycosides. The biological activity of cardiac glycosides is determined in the experiments on frogs (cardiac stop in systole), cats, and pigeons (cardiac stop in diastole).

Pharmacokinetics: Accordingly pharmacokinetics cardiac glycosides are divided into:

1. Polar glycosides (Strophanthinum, corglyconum) are destroyed in the stomach. They are not connected with proteins and are not biotransformed in organism, are excreted with urine and are not accumulated.

2. Relatively polar glycosides (Digoxinum, Celanidum, Infusum herbae Adonidis vernalis) which are partially absorbed and partially are connected with albumin, partially are biotransformed in liver, and less accumulate in comparison with Digitoxinum; they are excreted with urine and faeces.

3. Non-polar glycosides (Digitoxinum) are fully absorbed and firmly connected with proteins, biotransformed in liver, excreted first with bile and then are absorbed again and excreted with urine, faeces. These drugs are accumulated.

Pharmacologic effects: The most important property of cardiac glycosides is a **positive inotropic effect**, that is, their ability to increase the force of myocardial contraction. Glycosides also have effects on the electrophysiologic properties of the heart (conductivity, refractory period, and automaticity), negative chronotropic action (diastole lengthening and cardiac contractions frequency delaying); negative dromotropic action (conduction of impulses delaying). In low doses cardiac glycosides have negative batmotropic action, in high – positive batmotropic action which is characterized with increase of excitability of myocardial and special cells of myocardium (automatism). Cardiac glycosides increase the contractility of cardiac muscle by increasing both the velocity of muscle contraction and the maximum force which is developed. Cardiac glycosides do not prolong the duration of the contraction. In CHF patients, glycosides cause a shift in the ventricular function curve which increases cardiac output, decreases cardiac filling pressures, heart size, and venous

and capillary pressures. The drugs may normalize or increase arterial pressure.

Cardiac glycosides appear to exert their positive inotropic effect by some mechanisms:

1. Digitalis inhibits membrane-bound $\text{Na}^+\text{-K}^+$ -activated adenosine triphosphatase (Na^+ , K^+ -ATPase), decrease K^+ , increase Na^+ level, thus increasing intracellular Ca^{2+} level after $\text{Na}^+\text{-Ca}^{2+}$ exchange.
2. The movement of Ca^{2+} into the cell causes an increase in the slow inward Ca^{2+} current during the action potential by means of chelating with calcium. Digitalis may interfere with Ca^{2+} binding to the sarcoplasmic reticulum, making more Ca^{2+} available for interaction with contractile proteins.
3. By means of catecholamine liberation from depot and realization of cAMP depending mechanisms.

Cardiac glycosides may conform contractile proteins, raise their ability for interaction with calcium. There are data which cardiac glycosides may increase secretion of digitalis — like factor in myocardium. They have trophic effects on different sides of myocardium metabolism, stabilize lisosomes. The digitalis-induced increase in myocardial contractility causes an increase in myocardial oxygen consumption. Cardiac glycosides decrease frequency of cardiac contractions indirectly increasing a vagal tone of the heart. They prolong the refractory period of the atrioventricular (A-V) node and decrease conduction velocity (direct and indirect effects) through the A-V node. They liberate acetylcholine and may stimulate M_2 -cholinoreceptors. In CHF patients, digitalis slows the heart rate (a **negative chronotropic effect**). This is due to a combination of vagal and sinoatrial (S-A) nodes. When cardiac glycosides increase the cardiac output in CHF patients, there is a drop in peripheral vascular resistance and venomotor tone as well as an increase in blood flow. In normal individuals, digitalis produces venous and arterial constriction. Because digitalis increases the stroke volume in CHF patients, systolic blood pressure may rise. Diastolic pressure may fall because of improved circulation, increased tissue oxygenation, and diminished reflex vasoconstriction. Cardiac glycosides cause sedative effects connecting with blockade of $\text{K}^+\text{-Na}^+$ -ATP-ase of neurons. A diuretic

effect occurs because the increased cardiac output and renal blood flow combine to reduce the neurohumoral factors which inhibit the excretion of salt and water.

Therapeutic uses and contraindications. Cardiac glycosides are of greatest value for treating acute and chronic **low output cardiac failure**. They are also of great value in the **control of atrial fibrillation and flutter** because of the ability to reduce the ventricular rate by prolonging the refractory period of conduction tissue. **Paroxysmal atrial tachycardia** frequently responds to digitalis therapy, presumably as a result of reflex vagal stimulation.

The use of cardiac glycosides is **contraindicated** in cardiac tamponade, high-output CHF, constrictive pericarditis, and idiopathic hypertrophic subaortic stenosis with outlet obstruction.

Digoxinum. When there is no urgency, an **oral digitalizing dose** is first administered, and then the maintenance dose is adjusted on the basis of clinical and laboratory assessment. Usually a steady-state level is achieved in 5 half-lives (8 days). When digitalization must be achieved rapidly, digoxin can be administered intravenously over a period of several minutes. The onset of action is within 5-30 minutes; the maximal effect is reached within 1-5 hours. In chronic heart failure digoxinum is administered in supportive doses 2 times a day (0.0625-0.125 mg).

Digitoxinum has the most prominent bradycardic effect. The maximal effect of a dose of digitoxinum is reached approximately 9 hours after oral administration. In chronic heart failure if the nitrogen excreting function is damaged it is administered 2 times a day in supportive doses instead of digoxinum.

Strophanthinum K, Strophanthinum G, corglyconum have more systolic action than diastolic. Effect of strophanthinum begins in 2-10 minutes, that of corglyconum in 3-5 minutes, their duration is 30-120 minutes. Corglyconum is a neogalenic drug of *Convallaria majalis*, less toxic than strophanthinum. Strophanthinum and corglycone are used in acute cardiac insufficiency.

Celanidum acts quicker than digoxinum and accumulates less. It can be used in acute and chronic cardiac insufficiency.

Adverse effects: Digitalis glycosides have a low margin of safety and

intoxication from an excess of the drug is a common and potentially fatal problem. Signs of toxicity include: anorexia (often the earliest sign), nausea, vomiting, and diarrhea, headache, fatigue, malaise, neuralgias, and delirium; colour eyesight changes, gynecomastia (rare).

Cardiac effects are: premature ventricular contractions (PVCs), ventricular tachycardia and fibrillation, A-V dissociation and block, sinus arrhythmia and S-A block, paroxysmal and nonparoxysmal atrial tachycardia, often with A-V block.

Treatment of digitalis toxicity. Cardiac glycosides and K^+ -depleting diuretics are discontinued. KCl is administered orally or by slow, careful intravenous infusion if hypokalemia is present. Because hypomagnesaemia may accompany hypokalemia, magnesium replacement may also be necessary. It is better to administer asparkamum. Dipheninum can be given for ventricular and atrial arrhythmias. Lidocainum can be used to treat ventricular tachyarrhythmias. Atropini sulfas can be used to control sinus bradycardia and various degrees of A-V block. Carbo activatus absorbs and cholestyraminum binds to cardiac glycosides and they have been used to hasten their elimination. Vitamins and metabolites may be also administered. A digoxin-specific antibody fragments from immunized sheep, antidigoxin serum are available for the treatment of life-threatening digoxinum or digitoxinum overdose. Its use is reserved for patients exhibiting shock or cardiac arrest, ventricular arrhythmias, progressive bradyarrhythmias, or severe hyperkalemia. Electrical conversion is often hazardous in the treatment of digitalis-induced arrhythmias because it can precipitate ventricular fibrillation.

Nonglycosides cardiotonics

Phosphodiesterase Inhibitors: Amrinonum and milrinonum are the major representatives of this infrequently used group. These drugs increase cAMP by inhibiting phosphodiesterase type III and cause an increase in cardiac intracellular calcium similar to that produced by beta adrenoceptor agonists. The drugs exert positive inotropic effect. Phosphodiesterase inhibitors also cause vasodilation, which may be responsible for a major part of their beneficial effect. At sufficiently high concentrations these agents may increase the sensitivity of the contractile protein

system to calcium. These agents should not be used in chronic failure: they have been shown to increase morbidity and mortality.

Amrinonum and milrinonum are bipyridine derivatives. They are reserved for a short-term therapy of acute CHF which is refractory to other agents.

Adverse effects: A dose-related thrombocytopenia may occur. The drugs may increase the ventricular rate in patients with atrial flutter or fibrillation.

Simpathomimetics: Dophaminum stimulates dophamine, alpha- and beta₁-adrenoreceptors. It increases contractility arterial pressure, increases heart rate and kidney circulation.

Dobutaminum stimulates beta₁-adrenoreceptors. It increases contractility arterial pressure, increases heart rate. Indications of these drugs are hypotension, shock status, acute cardiac insufficiency.

The drugs of different mechanisms of action. Levosimendanum is calcium sensitiser, kalium channels activator, phosphodiesterase inhibitor. It is used in acute and chronic cardiac insufficiency.

	Drug	Drug forms
1.	Digitoxinum	Tab. 0,0001; Supp. 0,00015
2.	Digoxinum	Tab. 0,00025; Amp. 0,025 1ml
3.	Celanidum	Tab. 0,00025 Amp. 0,02% - 1ml
4.	Strophanthinum K	Amp. 0,05% -1ml 0,025% - 1ml
5.	Strophanthinum G	Amp. 0,05% -1ml 0,025% - 1ml
6.	Corglyconum	Amp. 0,06% - 1ml
7.	Infusum herbae Adonidis vernalis	Ex 6,0 – 180ml

8.	Dobutaminum	Amp. 0,1, 0,25
9.	Dophaminum	Amp. 0,5%, 4% - 5ml

DRUGS USED IN THE TREATMENT OF ARRHYTHMIA

Cardiac arrhythmias are abnormalities in the rate, regularity, or site of origin of the cardiac impulse, or a disturbance in conduction of the impulses. Arrhythmias may be due to: faulty impulse initiation, faulty impulse conduction, combinations of the above. The change in the impulse upsets the normal relationship which exists between the duration of the refractory period and the conduction velocity in myocardial tissue. The action potential of cardiac cells is divided into phases. The voltage changes of the action potential are associated with changes in ionic conductance across the cell membrane.

Phase 0. Rapid depolarization: Na^+ rapidly enters the cell through Na^+ -specific channels ("fast" channels) in the cell membrane.

Phase 1. Rapid repolarization: K^+ briefly leaves the cell.

Phase 2. Sustained depolarization (plateau): Ca^{2+} enters the cell through Ca^{2+} -specific channels ("slow" channels) in the cell membrane.

Phase 3. Rapid repolarization: K^+ leaves the cell.

Phase 4. Slow depolarization (diastole): In cells capable of self-excitation (e.g. His-Purkinje cells), several ionic currents flow into and out of the cell until an impulse is fired off. Other cells remain resting until activated.

Most antiarrhythmic agents depress the automaticity (i.e. decrease the rate of phase 4 depolarization) of latent pacemakers more effectively than of the S-A node. Inhibition of automaticity may also be due to a decreased threshold potential or decreased excitability of pacemaker cells. Disturbances in cardiac conductance may underlie supraventricular or ventricular arrhythmias. Antiarrhythmic drugs are the medicaments for prophylactic and treatment of arrhythmias.

There are group of **drugs for treatment of bradyarrhythmias:**

1. M-cholinoblockers – atropini sulfas, Tinctura Belladonnae, extractum

Belladonnae, guttae Zelenini;

2. Adrenomimetic drugs – adrenalini hydrochloridum, noradrenalini hydrotartars, isadrinum, orciprenalini sulfas;

3. Glucagonum (in some countries).

There are groups of **drugs for treatment of tachyarrhythmias** divided into classes of antiarrhythmic drugs.

Class I antiarrhythmic agents depress **phase 0** of the action potential by blocking Na^+ channels and is called membranostabilizers.

Class IA antiarrhythmics cause moderate phase 0 depression but prolong **repolarization**. Class IA drugs include chinidini sulfas, novocainamidum, and disopyramidum.

Class IB antiarrhythmics cause minimal phase 0 depression and shorten repolarization. Class IB drugs include lidocainum, dipheninum, mexiletinum, tocainidum, and trimecainum.

Class 1C antiarrhythmics cause marked phase 0 depression but have little effect on repolarization. Class 1C drugs include propaphenonum, flecainidum, aethacizinum, aethmozinum, aimalinum and encainidum.

Class II antiarrhythmic agents act by β -adrenergic blockade. Class II drugs includes propranololum, metoprololum, atenololum, betaxololum, acebutololum, and esmololum.

Class III antiarrhythmic agents prolong repolarization and lengthen phase 2 of the action potential by blocking K^+ -channels. Class III drugs includes amiodaronum and sotalolum.

Class IV antiarrhythmic agents are Ca^+ antagonists. Class IV drugs include verapamilum, diltiazemum, and others. Verapamilum is currently approved as an antiarrhythmic agent, while diltiazemum is currently being evaluated for supraventricular arrhythmias.

Others: cardiac glycosides, drugs of kalium, magnesium, metabolic and plunt drugs.

Class IA antiarrhythmic agents

Chinidini sulfas an alkaloid isolated from cinchona bark is the dimer of quinine.

Pharmacokinetics: Chinidini sulfas is well absorbed after oral administration. It exerts a maximum effect within 1-2 hours after administration by this route. It is metabolized in the liver and excreted by the kidneys.

Pharmacologic effects: At high concentrations, chinidini sulfas has direct effects on most cells of the heart. At lower concentrations indirect (anticholinergic) effects may significantly contribute to the overall action of chinidini sulfas on the heart. Chinidini sulfas is believed to block Na^+ channels. The major effect of chinidini sulfas is to reduce the maximal velocity of depolarization during phase 0 at all transmembrane voltages in atrial, ventricular, and Purkinje fibers. Automaticity is decreased in ventricular tissue by depression of the slope of phase. Chinidini sulfas has little effect on automaticity of the sinus node. Because chinidini sulfas depresses conduction in the bundle of His-Purkinje fibers, it produces progressive prolongation of the QRS complex. Prolongation of the Q-T interval and alterations in T waves are related to delayed repolarization. Prolongation of the P-R interval is caused by the direct effect of the drug on A-V conduction and the refractoriness of the A-V system. Chinidini sulfas can depress vascular smooth muscle tone, partially by α -adrenoreceptor blockade. This may contribute to a reduction in peripheral vascular resistance.

Therapeutic uses: Chinidini sulfas is primarily used chronically and prophylactically to prevent recurrences of paroxysmal supraventricular tachycardia due to A-V nodal reciprocating tachycardia or to Wolff-Parkinson-White syndrome. Chinidini sulfas can also be used to convert atrial flutter or fibrillation to normal sinus rhythm. Chinidini sulfas is now more frequently used to prevent recurrence of this arrhythmia. The drug should not be used without prior digitalization because its vagolytic action may increase the frequency of impulse transmission across the A-V node. Chinidini sulfas is very useful for a long-term treatment of ventricular premature depolarization or to prevent recurrences of ventricular tachycardia after cardioversion of this arrhythmia. Chinidini sulfas is usually given orally three or four

times a day.

Adverse effects: Cardiotoxicity includes A-V block, ventricular tachyarrhythmias, and depression of myocardial contractility. Increase in the QRS complex indicates the need for a prompt reduction in dosage. Diarrhea, vomiting, nausea, and anorexia are the most common side effects and when they are severe, one may force discontinuation of chinidini sulfas. Chinidini sulfas can cause cinchonism. Mild symptoms of this condition include tinnitus, hearing loss, vomiting, and diarrhea; severe symptoms include headache, diplopia, and photophobia, altered perception of color, confusion, and psychosis. Sensitivity phenomena, including thrombocytopenia, can occur. Chinidini sulfas can rare cause hypotension because of a decrease in arteriolar resistance.

Novocainamidum differs from novocainum only in that it contains an amide structure rather than an ester linkage; this difference protects it from enzymatic hydrolysis and frees it from most of the CNS effects of novocainum.

Pharmacokinetics: Novocainamidum may be administered orally, intravenously, or intramuscularly. It is rapidly absorbed after oral administration and, when capsules are used, normally has a peak effect in about 1 hour. However, absorption of the drug from the gastrointestinal tract may be impaired immediately after an acute myocardial infarction. The half-life of novocainamidum is approximately 3 hours. Approximately 15% of the drug is bound to plasma proteins. Novocainamidum is eliminated by both hepatic metabolism and renal excretion and renal failure can produce toxicity. From 50%-60% of an administered dose is excreted unchanged in the urine.

Pharmacologic effects: The direct cardiac effects of novocainamidum are quite similar to those of chinidini sulfas. Novocainamidum decreases automaticity and lengthens the duration of action potential and the effective refractory period in the atria and ventricles. It slows conduction in the atrium, A-V node, and ventricle.

Electrocardiographic effects are also very similar to those of chinidini sulfas. Novocainamidum, especially when given intravenously, can cause a drop in blood pressure, probably from peripheral vasodilation. Unlike chinidini sulfas,

novocainamidum does not have α -adrenergic blocking properties.

Therapeutic uses: The clinical uses of novocainamidum are similar to those of chinidini sulfas. Novocainamidum is particularly effective in promptly abolishing ventricular premature depolarizations and paroxysmal ventricular tachycardia.

Adverse effects: Acute novocainamidum toxicity can cause ventricular arrhythmia, ventricular fibrillation, and cardiac depression. Nausea, vomiting, diarrhea, and anorexia occur fairly frequently with oral administration of novocainamidum, but they occur much less commonly than with chinidini sulfas therapy. Mental confusion and psychosis have been reported but occur less commonly than with the chemically similar compounds novocainum and lidocainum. Hypersensitivity reactions are much more common than with chinidini sulfas. Fever, joint and muscle pain, and skin rashes may occur. Fatal agranulocytosis, a syndrome resembling systemic lupus erythematosus may take place. Hypotension can result, especially following intravenous administration. Novocainamidum can precipitate acute glaucoma and urinary retention.

Disopyramidum is well absorbed (83%) following oral administration. It is approved in the United States for oral administration in the treatment of ventricular arrhythmias as an alternative to chinidini sulfas and novocainamidum. It may be as effective as chinidini sulfas and novocainamidum against atrial arrhythmias.

Class IB antiarrhythmic agents

Lidocainum is an amide local anesthetic.

Pharmacokinetics: Lidocainum is rapidly metabolized by the hepatic microsomal enzyme system with 70% of the amount that enters the liver being metabolized in a single pass (first-pass metabolism). Reductions in hepatic blood flow or function will reduce lidocainum plasma clearance. Oral administration of lidocaine results in a very low plasma concentration because of the high percentage of the drug which is removed by hepatic metabolism before reaching the general circulation. Lidocainum has an elimination half-time of approximately 1½ hours. Nearly 70% of the drug is bound to plasma albumin.

Pharmacologic effects: Lidocainum does not affect sinus nodal pacemaker

discharge. It will depress the rate of phase 4 depolarization of Purkinje and atrial muscle fibers and, thus, depresses automaticity at these sites. Lidocainum has very little effect on these electrophysiological properties of the atria. In the His-Purkinje system, lidocainum reduces action potential amplitude and membrane responsiveness. The maximal velocity of phase 0 depolarization in normal Purkinje fibers is not as greatly depressed with lidocainum as it is with novocainamidum or chinidini sulfas. However, the maximal velocity of phase 0 is severely depressed in fibers with reduced resting membrane potentials and elevated content of extracellular K^+ . Lidocainum decreases the duration of action potential by blocking the Na^+ channel in depolarized cells; it also shortens the effective refractory period of Purkinje fibers. Unlike chinidini sulfas and novocainamidum, lidocainum produces very few changes in the electrocardiogram. Lidocainum has little effect on autonomic tone.

Therapeutic uses: The use of lidocainum as an antiarrhythmic agent is limited, even though lidocainum is very effective in treating ventricular arrhythmias. Because of its rapid onset and short duration of action the drug is particularly useful in treating these arrhythmias when they arise in emergency situations, such as open-heart surgery, digitalis intoxication, myocardial infarction. Lidocainum can be administered intravenously or intramuscularly. Lidocainum can also be given by continuous intravenous infusion.

Adverse effects: The CNS side effects of lidocainum can include drowsiness, paresthesias, decreased auditory function, convulsions, and respiratory arrest. Circulatory collapse can occur in patients with an acute myocardial infarction after a rapid, large intravenous injection.

Mexiletinum is an orally active congener of lidocainum. Unlike lidocainum, its first-pass metabolism is low. Mexiletinum is the most useful in suppressing symptomatic ventricular arrhythmias. Mexiletinum is given orally.

Dipheninum is most useful in treating ventricular arrhythmias. It is particularly useful for ventricular arrhythmias associated with digitalis toxicity or acute myocardial infarction. Dipheninum is most often administered by intermittent

intravenous injection. Orally, therapy is initiated with a loading dose, followed by maintenance oral therapy.

Class 1C antiarrhythmic agents

Flecainidum (tambocorum) and **encainidum** are indicated for use in patients with life-threatening arrhythmias, such as sustained ventricular tachycardia. These agents are no longer indicated for less severe ventricular arrhythmias because they can precipitate cardiac arrest. Both agents are administered orally. Encainidum is not used in Ukraine.

Aethmozinum (moracizinum) and **aethacizinum** are the phenothiazines derivatives. Aethmozinum is not used in Ukraine. It often has antiarrhythmic properties as drugs of classes IA, IB, IC, it decreases conduction velocity, excitation automatism. In some patients it may have hypertensive action, increases cardiac rhythm, and pulse. Aethacizinum is similar to aethmozinum, but has more duration of action. They are used in cases of ventricular arrhythmias.

Propaphenonum has properties of the classes IC, II, III, and IV. It stabilizes membranes, has β -blockers effects, blocks calcium channels and lengthens repolarization weekly. It is used in the case of ventricular arrhythmias.

Aimalinum (Gilurythmal) is an alkaloid of Rauwolfia with antiarrhythmic properties. Unlike reserpinum it has neither sedative nor antihypertensive effect: neogilurythenal is half-synthetic drug, more active than aimalinum, they are used in ventricular arrhythmias.

Class II antiarrhythmic agents: β -adrenergic antagonists (β -blockers)

The antiarrhythmic effects of **propranololum** are due primarily to β -receptor blockade but also result from a direct membrane effect. Propranololum, by blocking β -receptors in the S-A node and blocking sympathetic and hormonal influences on this structure, depresses S-A node firing and causes bradycardia. Automaticity is also depressed in Purkinje fibers. The major effect of propranololum, which underlies its use as an antiarrhythmic agent, is that it causes a substantial increase in the effective refractory period of the A-V node due to β blockade.

Class III antiarrhythmic agents

Sotalolol is a prototypical class III drug. Sotalolol is a chiral compound, i.e. it has two optical isomers. One isomer is an effective beta-blocker, and both isomers contribute to the antiarrhythmic action. The hallmark of class III drugs is prolongation of the action potential AP duration. This AP prolongation is caused by blockade of I_{Kr} potassium channels which are responsible for the repolarization of the action potential. The AP prolongation results in an increase in effective refractory period and reduces the ability of the heart to respond to rapid tachycardias. Sotalolol is more commonly used and is available by the oral route. Sotalolol may precipitate torsade de pointes arrhythmia as well as signs of excessive beta blockade such as sinus bradycardia or asthma.

Amiodaronum is an iodinated benzofuran derivative.

Pharmacokinetics: Amiodaronum is highly lipid-soluble; its half-life is 20-100 days.

Pharmacologic effects: Amiodaronum increases both the duration of active potential and the effective refractory period in ventricular and atrial muscle by blocking calcium channels mainly and calcium, sodium channels. It increases the P-R, QRS, and Q-T intervals. It decreases S-A node automaticity. It induces α - and β -adrenergic blockade glucagons receptors blockade by noncompetitive antagonism; therefore, it causes both systemic and coronary vasodilation, has antianginal action.

Therapeutic use: Amiodaronum suppresses premature ventricular contractions and ventricular tachycardia. Its use is reserved for the treatment of life-threatening ventricular arrhythmias refractory to other treatment.

Adverse effects may be the following: pulmonary fibrosis, which is usually reversible, cardiac effects, including sinus bradycardia, A-V block, paradoxical ventricular arrhythmias (torsades de pointes), photosensitivity, corneal microdeposits and blurred vision, hyper- or hypothyroidism - amiodarone interferes with conversion of thyroxine (T_4) to triiodothyronine (T_3). Neurologic effects, such as ataxia, dizziness, tremor, peripheral neuropathy, and proximal myopathy may be observed. Anorexia, nausea, vomiting, increases in serum levels of digitalis, diltiazemum,

chinidini sulfas, and novocainamidum may occur.

Class IV antiarrhythmic agents: calcium (Ca^{2+})-channel blockers

Verapamilum and **diltiazemum** are effective in arrhythmias which must traverse calcium-dependent cardiac tissue (e.g. cardiomyocytes, the atrioventricular node). These agents cause a state- and use-dependent selective depression of calcium current in tissues which require the participation of L-type calcium channels. Conduction velocity is decreased and effective refractory period is increased by these drugs. PQ interval is consistently increased.

Adenosinum: Adenosinum is a normal component of the body, but when it is given in high doses (6-12 mg) as an intravenous bolus the drug markedly slows conduction in the atrioventricular node, probably by hyperpolarizing this tissue (through increased I_{K1}) and by reducing calcium current. Adenosinum is extremely effective in abolishing A-V nodal arrhythmias and because of its very low toxicity has become the drug of choice for this arrhythmia. Adenosinum has an extremely short duration of action (about 15 seconds). Toxicity includes flushing and hypotension, but because of their short duration these effects do not limit the use of the drug. Chest pain and dyspnea may also occur.

Digitalis: The cardiac parasympathomimetic action of digoxin is sometimes exploited in the treatment of rapid atrial or A-V nodal arrhythmias. In atrial flutter or fibrillation, digitalis slows A-V conduction sufficiently to protect the ventricles from excessively high rates. In A-V nodal reentrant arrhythmias, digitalis may exert enough depressant effect to abolish the arrhythmia. The latter use of digitalis has become less common since the introduction of calcium channel blockers and adenosine as antiarrhythmic drugs.

Potassium Ion: Potassium depresses ectopic pacemakers, including those caused by digitalis toxicity. Hypokalemia is associated with an increased incidence of arrhythmias, especially in patients receiving digitalis. Conversely, excessive potassium levels depress conduction and can cause reentry arrhythmias. Therefore, when treating arrhythmias, serum potassium should be measured and, if abnormal, normalized.

Magnesium ion: Magnesium has not been as well studied as potassium but appears to have similar depressant effects on digitalis-induced arrhythmias. Magnesium also appears to be effective in some cases of torsade de pointes arrhythmia.

Metabolic drugs: ATP-long, neotonum (phosphocreatinum), asparkamum, riboxinum, rythmocorum and plant drugs: extractum Crataegi fluidum have also antiarrhythmic effects.

№	Drug	Drug forms
1.	Chinidini sulfas	Tab. 0,1, 0,2
2.	Novocainamidum	?? Tab. 0,25, 0,5; ?? Amp. 10% - 5ml
3.	Lidocaini hydrochloridum	Amp. 1% - 10ml 2% - 2, 10ml 10% - 2ml
4.	Aetmozinum	Tab. 0,1 Amp. 2,5% - 2ml
5.	Aethacizinum	Tab. 0,05; Amp. 2,5% - 2ml
6.	Propafenoni hydrochloridum	Tab. 0,15, 0,3; Amp. 0,035 – 10ml 0,07 – 20ml
7.	Ajmalinum	Tab. 0,05; Amp. 2,5% - 2ml
8.	Amiodaronum	Tab. 0,2; Amp. 5% - 3ml
9.	Kalii chloridum	Amp. 4% - 50ml; Sol. 10%
10.	Pananginum	Dragée; Amp. 10ml

11. Extractum Crataegi Flac. 25ml
fluidum

DRUGS USED IN THE TREATMENT OF ANGINA AND OTHER VASODILATORS

The nitrates, the β -adrenergic antagonists, and the Ca^{2+} -channel blockers are the main drugs which are useful in treating the pain resulting from ischemic heart disease. They provide symptomatic treatment of angina pectoris but do not affect the course of the disorder. Several vasodilators which are not used in the treatment of angina are also briefly discussed in this section.

There are different groups of antianginal drugs:

1. Drugs which decrease the need of myocardium in oxygen and improve blood circulation (organic nitrates, calcium channels blockers, drugs of different groups - molsidominum, amiodaronum);
2. Drugs which decrease the need of myocardium in oxygen;
3. Drugs which improve blood circulation:
 - a. Myotropic vasodilators drugs, blockers of phosphodiesterase (papaverini hydrochloridum, no-spanum, pentoxyphyllinum);
 - b. Drugs of reflex action on coronar vessels (validolum) influencing on cold receptors of mouth;
 - c. Antiagregants (dipyridamolum, acidum acetylsalicylicum, ticlopidinum, clopidogrelum, integrininum, and eptifibatidum).
4. Drugs which increase stability of organism to hypoxia:
 - a. Ergooverneubum drugs – trimetazidinum, mildronatum, neotonum, ATP, ATP-long, cratalum, asparkamum, and rythmocorum;
 - b. Electronacceptors – acidum ascorbinicum, cytochromum C, and riboflavinum;
 - c. Antioxydant drugs – tocoferoli acetas, quercetinum, corvitinum, lipinum, lipoflavinum, thiotriazolinum;
 - d. Anabolic drugs – steroid and nonsteroid structures (riboxinum, kalii orotas, magnerotum, retabolilum, nerobolum).

Drugs which decrease need of myocardium in oxygen and improve blood circulation

Organic nitrates

Glyceryl trinitrate (**nitroglycerinum**) is a prototype of this group, which has been known since 1864.

Mechanism of action: The nitrates relax all smooth muscle, including vascular smooth muscle. The proposed biochemical action involves the formation of free radical nitric oxide (NO), endothelial-derived relaxation factor (EDRF), which stimulates guanylate cyclase. The resultant guanosine 3', 5'-monophosphate (cyclic GMP) activates a protein kinase, which mediates dephosphorylation of myosin. They reduce mainly venous tone, thereby increasing venous capacitance return to the heart, block calcium influx, the properties of emtracties protein. They decrease mainly systemic peripheral arteriolar resistance.

Pharmacokinetics: The nitrates are readily absorbed through the buccal mucous membranes, skin, gastrointestinal tract, and the lungs. Sublingual administration produces rapid onset (2-5 minutes) and short duration of action (less than 30 minutes) and, thus, provides the best treatment for acute attacks of angina. Oral preparations of nitroglycerinum (e.g. sustac mitte, sustac forte, nitrong etc), which often come in a sustained-release form and have onset of action 20-45 min, can provide more prolonged prophylaxis (3-6-8 hours) against angina than sublingual forms. The nitrates are broken down in the liver by a glutathione-dependent organic nitrate reductase and are excreted in the form of various nitrites and nitrates.

Pharmacologic effects: The major effect of the nitrates on the heart is to reduce myocardial oxygen requirements relative to myocardial oxygen delivery. The arterial dilation produced by nitrates causes a reduction in the mean systemic arterial pressure, which reduces the afterload of the heart and, thus, diminishes the oxygen requirements of the heart. The venous dilation produced by nitrates results in increased peripheral pooling of blood, which decreases ventricular end-diastolic pressure and volume (decreased preload). This reduction in ventricular pressure and size results in a decreased myocardial wall tension and, therefore, in decreased

oxygen requirements. The decrease in left ventricular end-diastolic pressure reduces tissue pressure around subendocardial vessels, favoring the redistribution of coronary blood flow to this area. Nitrates are believed to dilate the large epicardial and collateral coronary arteries selectively, an action which favors the distribution of blood to ischemic areas. Vasodilation of cerebral vessels produced by nitrates results in increased intracerebral pressure and sometimes in headache. The nitrates dilate vessels in the skin, resulting in flushing. They relax bronchial and biliary tract smooth muscle with the latter action resulting in a reduction of biliary pressure.

Nitroglycerinum (glyceryl trinitrate) is usually given sublingually, in tablets, capsules, spray. However, for long-lasting effects, nitroglycerinum may be administered either orally in retard tablets and capsules or topically (**transdermally**) via ointment or patch, transdermal transport systems. Nitroglycerinum may also be given intravenously in medical emergencies

Therapeutic uses: The primary use of nitrates is to treat acute attacks of angina pectoris and its prolonged forms in anticipation of attacks, to prevent their occurrence. Nitroglycerinum is in sublingual tablets, spray, injections is used to treat cardiac infarction and hearts failure. Paroxysmal nocturnal dyspnea can be relieved with nitroglycerinum by improving left ventricular pressure and reducing pulmonary pressure.

Adverse effects: Headache is a common early side effect of nitrates which usually decreases after the first few days of treatment (i.e. patients usually develop a tolerance to headache). Temporarily discontinuing drugs for a few days causes a recurrence of susceptibility to headache. Decreasing a dose of nitrates, combinations with non-narcotic analgetics are sometimes beneficial for headache. Dizziness, weakness, and cerebral ischemia associated with postural hypotension occasionally occur. Nitrite ions, when present in large amounts, can oxidize enough hemoglobin to methemoglobin to result in hypoxia. Death can occur with acute nitrate poisoning from circulatory collapse or respiratory failure. When nitrates are appropriately administered intermittently in small doses, with thiodrugs (antioxidants) tolerance does not occur.

Isosorbidi dinitras in sublingual form has onset of action 3-20 minutes, duration of action 1-2 hours, oral form - 30-60 minutes and 2-10 hours; oral sustained release form - 30-60 minutes and 6-10 hours accordingly. The drug is used in treatment of angina pectoris and in cardiac insufficiency.

Isosorbidi mononitras in oral form begins to act in 15-30 minutes, duration of action 6-12 hours. Oral tablets are used for protection angina pectoris attacks and treatment of heart failure.

Calcium channel-blocking drugs

The calcium channel blockers are divided into three groups:

1. Derivatives of phenylalkylamines: verapamilum, galopamilum, bepridilum;
2. Derivatives of dihydropyridines: nifedipinum, foridonum, amlodipinum, nicardipinum, felodipinum, lacidipinum, lercanidipinum, and manidipinum
3. Derivatives of benzothiazepinum: diltiazemum.

There are three generations of calcium blockers. The first generation is characterized by short action and unstable pharmacokinetics. Verapamilum, nifedipinum, foridonum, and diltiazemum are belonged to the first generation. The second generation includes drugs of the same structures, but with long action and slow releasing (e.g. nifedipinum retard). The third generation of drugs has original structure, for example amlodipinum, felodipinum etc.

Ca²⁺-channel blockers of first generation (verapamilum, nifedipinum, diltiazemum, and nicardipinum) are approved for use in angina; diltiazemum and verapamilum half-lives of 3-6 hours. These drugs block voltage-gated "L-type" calcium channels, the calcium channels most important in cardiac and smooth muscle. By decreasing calcium influx during an action potential in a frequency- and voltage-dependent manner, these agents reduce intracellular calcium concentration and muscle contractility.

Pharmacokinetics: Verapamilum, diltiazemum, nifedipinum, and nicardipinum are rapidly and almost fully absorbed after oral administration. The drugs of the second and third generations are absorbed slowly. Peak blood levels of nifedipinum occur in about 30 minutes; peak levels of diltiazemum occur in about 1

hour, and peak levels of verapamil occur in 1-2 hours. A stable level of plasma half-life of nifedipine is 8-9 hours. All four drugs are highly bound by serum proteins. Verapamil undergoes extensive first-pass biotransformation in the liver. All four drugs are excreted as metabolites in the urine.

Pharmacologic effects: Ca²⁺-channel blockers have diverse effects on the cardiovascular system. They dilate the main coronary arteries and coronary arterioles, and by inhibiting coronary artery spasm, they increase myocardial oxygen delivery in patients with Prinzmetal's angina. The drugs dilate peripheral arterioles and reduce the total peripheral vascular resistance, therefore reducing the oxygen requirements of the myocardium. Calcium blockers relax blood vessels and, to a lesser extent, the uterus, bronchi, and gut. The rate and contractility of the heart are reduced by diltiazem and verapamil. The drugs (Verapamil, Diltiazem) slow A-V and S-A node conduction and prolong the effective refractory period within the A-V node; verapamil and diltiazem seem to have a greater effect on these parameters in clinical situations. Nifedipine reduces cardiac preload and may actually increase the heart rate. Diltiazem influences the vessels less than derivatives of dihydropyridines and less decreases calcium influx into myocardial cells than verapamil. It decreases or does not change cardiac output, has negative inotropic effect, decreases coronary arteries tonus, peripheral vessels resistance, increases sympathetic activity.

Amlodipine, a derivative of dihydropyridines, contrary to nifedipine is absorbed more fully and slower, connected with albumins of plasma stronger, biotransforms minimally, has long period of half excretion. Amlodipine does not cause tachycardia or causes very seldom. These agents have also been shown to antagonize the aggregation of thrombocytes and, thus, to inhibit the release of thromboxane A₂ (TXA₂). They have sedative and spasmolytic effects. Verapamil produces nonspecific sympathetic antagonism and has a local anesthetic effect.

Ca²⁺- channel blockers may be given orally, in tablets, verapamil is also available in intravenous form.

Therapeutic uses: Ca²⁺-channel blockers are useful in the treatment of both

Prinzmetal's (variant) angina and classic stable angina. Nifedipinum appears to be the most effective for Prinzmetal's angina.

Adverse effects: The Ca^{2+} -channel blockers, perhaps especially when used in combination with β -adrenergic blocking agents, can produce or aggravate the following: hypotension, A-V block, congestive heart failure, asystole, dizziness and peripheral edema are among the more common.

Treatment with verapamilum increases serum levels of digitalis during the first week of therapy and, thus, can cause digitalis toxicity.

Drugs of other structure

Molsidominum acts due to biotransformation into NO, and is designed in case of ischaemic heart diseases and heart failure. Amiodaronum has antiarrhythmic and antianginal effects but is used as an antiarrhythmic drug.

Drugs decreasing myocardium need in oxygen

β -adrenoblockers such as metoprololum, atenololum, betaxololum, bisoprololum are used to decrease severity and frequency of anginal attacks. Metoprololum is absorbed very quickly. It is used perorally and intravenously. It penetrates through haematoencephalic barrier. Metoprololum in prolonged form is used for treatment patients with cardiac insufficiency. Atenololum acts longer than metoprololum, does not penetrate through haematoencephalic barrier and disturb sleep and emotional sphere. Bisoprololum acts longer than atenololum and does not disturb lipid and carbohydrate metabolism.

Vasodilators increasing oxygenation, circulation of myocardium

Dipyridamolum concurrent inhibits adenosinedesaminase increases level of adenosine. By inhibiting the uptake of adenosine into erythrocytes and other tissues, dipyridamolum allows metabolically released adenosine, which is a coronary vasodilator, to accumulate in the plasma. The drug decreases coronary vascular resistance and increases coronary blood flow and coronary sinus oxygen saturation. (Dipyridamolum also inhibits in vitro platelet aggregation, increases prostacycline level, inhibits thromboxane synthesis and can be used to prevent the formation of thromboemboli in patients with prosthetic cardiac valves.)

It may decrease circulation in ischemic part.

№	Drug	Drug forms
1.	Nitroglycerinum	Tab., caps. 0,0005; Amp. 0,1% - 10ml, 0,05 %– 25ml; Flac. sol. spirit. 1% - 10ml
2.	Sustac-mite	Tab. 0,0026 Nitroglycerini
3.	Sustac-forte	Tab. 0,0064 Nitroglycerini
4.	Nitrosorbidum	Tab. 0,005; 0,01; 0,02; Amp. 0,1% - 10ml
5.	Isosorbidi mononitras	Tab. 0,02, 0,04; Amp. 1% - 1ml
6.	Molsidominum	Tab. 0,002, 0,004
7.	Validolum	Tab. 0,06; Flac. 5ml
8.	Nifedipinum	Tab. 0,01, 0,02
9.	Anaprilinum	Tab. 0,01, 0,04; Amp. 0,1% - 1ml, 5ml
10.	Metoprololum	Tab. 0,05, 0,1; Amp. 1% - 5ml
11.	Atenololum	Tab. 0,05, 0,1
12.	Riboxinum	Tab. 0,2; Amp. 2% - 10ml

DRUGS USED IN THE TREATMENT OF HYPERTENSION

There are two classifications of antihypertensive drugs – pharmacological and clinical.

Pharmacological classification includes neurotropic drugs, drugs of myotropic action, calcium blocking drugs, diuretics, drugs which influence the angiotensin system.

The clinical classification distinguishes main and additional groups of drugs. The main group includes diuretics, β -adrenoblockers, calcium channels blockers, angiotensin converting enzyme inhibitors, and angiotensin receptors antagonists. The additional group includes the CNS-active agents, ganglionic blocking agents, sympathetic nerve terminal blockers, α_1 -adrenoreceptor blockers, vasodilators, central α_2 -receptor agonists, and imidazoline receptor agonists.

Traditionally the first choice for the initial treatment of chronic hypertension has been a thiazide-type diuretic or a β -adrenergic receptor blocker. More recently some physicians prefer to start therapy with an ACE inhibitor angiotensin receptors antagonists, or Ca^{2+} -channel blocker.

In **hypertensive emergencies**, parenteral therapy is indicated, usually with natrii nitroprussidum or diazoxidum; intravenous labetalolum ganglioblockers – benzohexonium, pentaminum; diuretics – furosemidum, torasemidum, β -adrenoblockers – propranololum, metaprololum or sublingual nifedipinum, chlomidinum, captoprylum are also suitable. Oral therapy should be started as soon as possible because parenteral therapy is not suitable for a long-term management of hypertension.

Diuretic agents

Diuretics are useful antihypertensive drugs when employed alone, as well as when used in combination therapy, where they potentiate the action of other hypotensive drugs. Antihypertensive action resulted from their ability to produce a negative Na^+ balance. These drugs lower blood pressure by reduction of blood volume

and by a direct vascular effect. The diuretics most important for treating hypertension are the **thiazides** (e.g. hydrochlorothiazidum) drugs similar to thiazidum (e.g. nidadamidum and clopamidum) and the **loop diuretics** (e.g. furosemidum). Thiazides may be adequate in mild hypertension, but the loop agents are used in moderate, severe, and malignant hypertension. The thiazides and thiazidelike diuretics are the most frequently used diuretics. Their early hypotensive effect is related to a reduction in blood volume; their long-term effect is related to a reduction in peripheral vascular resistance.

Furosemidum, acidum ethacrynicum, torasemidum and bumetanidum produce greater diuresis than the thiazides, but they have a weaker antihypertensive effect and can cause severe electrolyte imbalance. Because they retain their effectiveness in the presence of impaired renal function, they are useful in cases where renal function is so impaired that the thiazides can no longer promote sodium excretion.

Spirolactonum, eplerenonum, triamterenum, and amiloridum have modest hypotensive and diuretic effects and are useful in combination with thiazide diuretics, whose effects they potentiate and where they minimize K^+ loss. Spirolactonum and eplerenonum are useful in treating patients whose hypertension is due to mineralocorticoid excess

Adrenoceptor Blockers

Alpha₁-selective agents (e.g. **prazosinum, doxazosinum, and terazosinum**) and beta-blockers (e.g. **propranololum, atenololum, metoprololum, bisoprololum, betaxolum, nebivololum, and celiprololum**) are effective antihypertensive drugs. Alpha-blockers reduce vascular resistance and venous return. The nonselective alpha-blockers (phentolamini sulfas and pyrroxanum) are of no value in chronic hypertension because of excessive compensatory responses, especially tachycardia. Alpha₁-selective adrenoceptor blockers are relatively free of the severe adverse effects of the nonselective alpha-blockers and postganglionic nerve terminal sympathoplegic agents.

Beta-blockers initially reduce cardiac output, but after a few days their action

may include a decrease in vascular resistance as a contributing effect. The latter effect may result from reduced angiotensin levels (beta-blockers reduce renin release from the kidney). The beta-blockers are among the most heavily used antihypertensive drugs. Beta-blocker therapy is associated with slightly elevated low density lipids and triglyceride concentrations and diminished high density lipids levels in the blood.

1. These agents are useful both alone and in combination with antihypertensive therapy.
2. Their mechanism of action in hypertension is connected with:
 - a. The β -blockers reduce cardiac output;
 - b. They also inhibit renin secretion.

Sympathetic selectivity. The various β -blockers all appear to be equally effective for the treatment of hypertension. However, they vary in their selectivity for adrenoceptors.

Propranolol, timolol, nadolol, pindolol, penbutolol, and carteolol are nonselective, while metoprolol, acebutolol, atenolol, betaxolol, bisoprolol, nebivolol, celiprolol, talinolol, and esmolol are cardioselective (i.e. they have a greater effect on β_1 adrenoceptors).

Talinolol, celiprolol, esmolol, pindolol, acebutolol, penbutolol, and carteolol also have intrinsic sympathomimetic activity. They decrease blood pressure with less of a decrease in cardiac output or heart rate at rest. They are also unlikely to cause serum lipid abnormalities.

Labetalol and carvedilol are nonselective β -blocker, and block vascular postsynaptic α -adrenergic receptors. Carvedilol has antioxidant properties.

Adverse effects: The β -adrenergic receptor antagonists can exacerbate congestive heart failure, asthma, and chronic obstructive pulmonary disease. They can mask symptoms of hypoglycemia in individuals with diabetes mellitus. They can increase serum triglycerides and decrease high-density lipoprotein cholesterol (exceptions are β -blockers with intrinsic sympathomimetic activity). Labetalol,

when used chronically, causes more frequent orthostatic hypotension and sexual dysfunction than other β -adrenoblockers do.

Calcium Channel-Blocking Agents

Calcium channel blockers (e.g. nifedipinum, verapamilum, foridonum, nicardipinum, amlodipinum, felodipinum, lacidipinum, lercanidipinum, manidipinum, and diltiazemum) are effective vasodilators, because they are orally active. These drugs are suitable for chronic use in hypertension of any severity. Nifedipinum is used in combination connecting with tachycardia. Nifedipinum sustained release and retard are available for treatment. Diltiazemum, verapamilum, and nicardipinum increase vasodilation and decrease peripheral resistance. Verapamilum and diltiazemum cause little change in heart rate, while nicardipine produces an initial increase, which is reflex-mediated. Diltiazemum and verapamilum depress A-V conduction and should not be used with β -blockers. Diuretics may enhance the efficacy of Ca^{2+} -channel blockers.

The choice of calcium channel blockers especially for combination therapy, is largely influenced by the effect of the drug on cardiac pacemakers and contractility and coexisting diseases such as angina, asthma, peripheral vascular diseases.

Vasodilators

Drugs which dilate blood vessels by acting directly on smooth muscle cells through nonautonomic mechanisms are useful in treating many hypertensive patients. Three major mechanisms are utilized by vasodilators: release of nitric oxide, opening of potassium channels (which leads to hyperpolarization), and blockade of calcium channels. **Arteriolar vasodilators** directly relax arteriolar smooth muscle and, thus, decreases peripheral vascular resistance and arterial blood pressure. The beneficial effect of these drugs on peripheral vascular resistance can be partially negated by the increased reflex sympathetic activity they produce, which can result in increased heart rate, stroke volume, and cardiac output. These drugs also can increase plasma renin activity as a result of increased reflex sympathetic discharge, causing a pressor effect. This group of drugs often causes salt and water retention and, thus, expansion of the extracellular fluid and plasma volume. Therefore, arteriolar vasodilators should

be used in conjunction with diuretic and β -adrenergic blocking therapy.

Apressinum (hydralazinum) has a greater effect on arterioles than on veins (which minimizes the incidence of postural hypotension). It may reduce diastolic more than systolic blood pressure. It may block phosphodiesterase.

Apressinum can be given orally or intramuscularly.

Therapeutic uses: Apressinum is used to treat moderate to severe hypertension, in the treatment of acute and chronic congestive heart failure, is combined with a β -adrenoblockers to prevent tachycardia and increased renin secretion due to reflex sympathetic stimulation, with a diuretic agent to prevent salt and water retention and with isosorbidi dinitras to combine influence on veins and arteries.

Adverse effects: Headache, anorexia, nausea, dizziness, and sweating occur frequently but tend to diminish as apressinum is administered over a period of time. Apressinum can worsen coronary artery disease because of the myocardial stimulation it produces. Apressinum can cause a reversible lupus-like syndrome, especially when more than 400 mg/day are administered to slow acetylators of the drug.

Arterial and venous vasodilators reduce both arterial resistance and venous tone and markedly decrease arterial blood pressure.

Natrii nitroprussidum is used in hypertensive emergencies. Natrii nitroprussidum is a short-acting agent (duration of action is a few minutes) which must be infused continuously. The drug mechanism of action involves the release of nitric oxide (from the molecule itself, not from the endothelium), which stimulates guanylyl cyclase and increases cGMP concentration in smooth muscle. The toxicity of nitroprusside includes excessive hypotension, tachycardia, and, if infusion is continued over several days, accumulation of cyanide or thiocyanate ions in the blood.

Pharmacokinetics: Onset of action occurs within 1 minute of intravenous administration, and effects cease within 5 minutes of stopping an infusion. The drug is rapidly inactivated by hepatic enzymes, first to cyanide and then to thiocyanate.

Pharmacologic effects: Natrii nitroprussidum acts directly on arterial and

venous smooth muscle but has little effect on other smooth muscle. It decreases blood pressure in both the supine and upright positions. The increased venous capacitance that it produces results in decreased cardiac preload and, thus, decreases myocardial oxygen demand for a given output. Natrii nitroprussidum causes a slight increase in heart rate and decrease in cardiac output except when heart failure is present. In the latter case the heart rate may decrease and the cardiac output increase. Renal blood flow is maintained with natrii nitroprussidum and renin secretion is increased.

Natrii nitroprussidum is administered only as an intravenous infusion with sterile 5% dextrose in water.

Therapeutic uses: Natrii nitroprussidum, like diazoxidum, is used for a short-term, rapid reduction of blood pressure in hypertensive emergencies. It is preferable to diazoxidum for treating hypertensive emergencies in patients with coronary insufficiency or pulmonary edema because, in contrast to diazoxidum, it reduces cardiac preload (by increasing venous capacitance) and, thus, myocardial oxygen demand. Natrii nitroprussidum can also be used to produce controlled hypotension to minimize bleeding during surgery. Natrii nitroprussidum can improve left ventricular function (lower ventricular filling pressure) in patients with acute myocardial infarction and has beneficial hemodynamic effects in the treatment of acute congestive heart failure.

Adverse effects: Hypotension, nausea, diaphoresis, headache, restlessness, palpitations, and retrosternal pain can occur secondary to excessive, rapid vasodilation. The rate of conversion of natrii nitroprussidum from its metabolite cyanide to thiocyanate is dependent on the availability of sulfur (usually as thiosulfate). Rarely, when high doses of natrii nitroprussidum are administered for a prolonged period and sulfur stores are low, cyanide toxicity can occur. Because thiocyanate is cleared slowly by the kidneys, it can accumulate during prolonged natrii nitroprussidum therapy, especially in patients with poor renal function. A plasma thiocyanate concentration of greater than 10 mg/dl can cause weakness, nausea, muscle spasms, and psychosis, as well as hypothyroidism due to interference with iodine transport. A case of methemoglobinemia following prolonged infusion of

natrii nitroprussidum has been reported.

Prazosinum. This quinazoline derivative is a selective postsynaptic α_1 -adrenergic receptor blocking agent which causes vasodilation both of arteries and veins.

Pharmacokinetics: Prazosinum is highly bound to plasma protein. Its plasma concentration peaks in about 3 hours. Plasma half-life is usually 2-3 hours but can be prolonged by congestive heart failure. Prazosinum is extensively metabolized, may undergo significant first-pass metabolism, has a bioavailability of about 60%, and is probably excreted in the faeces and bile.

Pharmacologic effects: Prazosinum reduces peripheral vascular resistance and lowers arterial blood pressure in both supine and erect patients. Unlike nonselective α -adrenergic blockers it does not usually produce reflex tachycardia. Prazosinum seems to produce minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Prazosinum is given orally, two or three times a day.

Therapeutic uses: Prazosinum is used to treat mild to moderate hypertension. It may be more effective in combination with a diuretics or β -adrenoblocking agents than when used alone. It is also sometimes used in the treatment of acute congestive heart failure.

Adverse effects: Dizziness, headache, drowsiness, and palpitations can occur but often disappear with continued therapy and rarely cause discontinuation of the drug. The initial dose of prazosinum, especially if larger than 1 mg can induce postural hypotension and syncope, probably due to decreased venous return to the heart. It is, therefore, best to give the initial dose at bedtime.

Centrally acting sympatholytic agents

Clophelinum and methyldopha act centrally on the vasomotor centers of the brain and are predominantly **α_2 -receptor agonists**, cause a decrease in sympathetic outflow to the peripheral vessels by a mechanism which involves activation of α_2 receptors in the CNS. Both clophelinum and methyldopha reduce blood pressure by reducing cardiac output, vascular resistance, or both. The major compensatory response

is salt retention. Sudden discontinuation of clophelinum causes rebound hypertension, which may be quite severe. Both drugs (but methyldopa to more extent) may cause sedation.

Clophelinum is imidazoline derivative to stimulate α -adrenergic receptors (probably presynaptic α_2 receptors) in the vasomotor centers of the brain, resulting in decreased sympathetic outflow to the peripheral vessels.

Pharmacokinetics: The antihypertensive effects of clophelinum develop within 30-60 minutes of oral administration, peak in 2-4 hours, and last approximately for 8 hours. The drug and its metabolites are excreted primarily in the urine.

Pharmacologic effects: Intravenous injection of clophelinum causes an initial increase in both systolic and diastolic pressure; oral administration does not normally produce this hypertensive effect. The initial rise in blood pressure is caused by direct stimulation of peripheral α -adrenergic receptors, producing transient vasoconstriction. Clophelinum also causes peripheral α -adrenergic blockade, and thus, it is a partial agonist. The increase in blood pressure following intravenous injection is transient and is soon followed by a fall in blood pressure, resulting from a decrease in cardiac output and heart rate, usually not accompanied by a significant change in peripheral resistance. Vagal discharge is increased by clophelinum in association with increased **baroreceptor** reflex sensitivity. Clophelinum decreases intraocular pressure. Clophelinum does not block the homeostatic control mechanisms of the peripheral autonomic system. It decreases plasma renin activity, primarily through a centrally mediated decrease in sympathetic stimulation of the juxtaglomerular cells of the kidney. Renal vascular resistance decreases, while renal blood flow remains essentially unchanged.

Clophelinum is given orally, parenterally, in eye drops. Clophelinum is also available as a transdermal patch, which is applied once in a week.

Therapeutic uses: Now clophelinum can be used to treat mild hypertension or moderate to severe hypertension very seldom. It indicates for treatment hypertensive

emergencies and narcomania. It may be used as a single agent or in combination with other antihypertensive agents. In eye drops it is used in glaucoma.

Adverse effects: Dry mouth, drowsiness, and sedation are the most frequent problems and may require discontinuation of clophelinum. Rebound hypertensive crises can result from abrupt cessation of clophelinum tablets or patches when the drug is used as a single agent. Fluid retention often occurs, requiring concurrent diuretic therapy. Clophelinum can cause or worsen depression.

Angiotensin antagonists

The kidneys synthesize renin, which acts on a plasma globulin substrate to produce angiotensin I. This, in turn, is converted (by a peptidyl dipeptidase) to angiotensin II, a potent vasoconstrictor. Angiotensin antagonists exert an antihypertensive effect by interfering with either the formation or the utilization of angiotensin II. The two primary groups of angiotensin antagonists are the **ACE inhibitors** and the **angiotensin II receptor antagonists**. Of these, the more extensively used are the ACE inhibitors (e.g. **captoprylum**), which inhibit the enzyme variously known as angiotensin-converting enzyme, kininase II, and peptidyl dipeptidase. The result is a **reduction** in blood levels of angiotensin II and aldosterone and probably an **increase** in endogenous vasodilators of the kinin family (bradykinin). The second group of angiotensin antagonists, the receptor antagonists, are represented by the orally active agents **losartanum** and its several analogues plus an older parenteral drug, **saralasinum**, which competitively inhibit connection of angiotensin II with its AT₁ receptor. Losartanum, valsartanum, irbesartanum, candesartanum, telmisartanum and other analogues appear to be as effective in lowering blood pressure as the ACE inhibitors and have the advantage of a much lower incidence of cough. However, they do cause fetal renal toxicity like that of the ACE inhibitors and are thus contraindicated in pregnancy.

Inhibitors of the ACE are divided into

1. Drugs which have SH-group – captoprylum, sopenoprilum;
2. Drugs which have carbonyl group – enalaprylum, lisinoprylum, celasoprilum, ramiprilum, perindoprinum, trandaloprylum, spiraprylum, and

quadroprylum;

3. Drugs which have phosphoryl group – phosynoprilum (monoprilum).

Captoprylum is transformed into inactive compound. Enalaprilum, ramiprilum, spiraprilum, trandaloprylum, and cilasoprylum are prodrugs. They are biotransformed in an active form. Phosynoprilum and quadroprilum are transformed into active compounds. Lisinoprilum is not biotransformed in organism. Lisinoprilum is one hydrophilic compound. Monoprilum, quadroprylum are transformed in liver and kidney.

Mechanism of action: Captoprilum, enalaprilum, lisinoprilum and other drugs are specific competitive inhibitors of peptidyl dipeptidase (an ACE), the enzyme which converts angiotensin I to angiotensin II. Angiotensin II is a potent direct vasoconstrictor. Thus, captoprilum, enalaprilum, and lisinoprilum inhibit vasoconstriction. Angiotensin II stimulates the secretion of aldosterone, which promotes salt and water retention. Thus, captoprilum, enalaprilum, and lisinoprilum inhibit the secretion aldosterone salt and water retention and slightly increase serum K^+ levels. The drugs decrease level of renin, aldosterone, endotheline-1, vasopressine, noradrenaline. Because peptidyl dipeptidase is necessary to catalyze the degradation of bradykinin, the ACE inhibitors may increase the concentration of bradykinin, which is a potent vasodilator, nitric oxide, prostaglandinum E_2 , I_2 . The ACE inhibitors also exert an antihypertensive effect in low-renin hypertension.

Pharmacokinetics: Captoprylum is rapidly absorbed following oral administration and reaches peak blood levels within an hour. Approximately 95% of a dose is eliminated by the kidneys within 24 hours. Enalaprilum is more potent than captoprilum and its duration of action is more than 24 hours, twice as long as that of captoprilum. Lisinoprilum is absorbed more slowly than enalaprilum and has a slower onset of action.

Pharmacologic effects: The cardiovascular effects of captoprilum and enalaprilum include a reduction in total peripheral resistance and mean arterial blood pressure preload, postload and either no change or an increase in cardiac output. Captoprilum is given orally 1 hour before meals. The initial dose can be increased at

1- to 2-week intervals. Enalaprilum is given orally once or twice a day, enalaprilatum is administered parenterally. Lisinoprilum is given orally once a day.

Therapeutic uses: The ACE inhibitors are increasingly used for the treatment of mild to moderate hypertension. The ACE inhibitors are effective for low-renin, as well as high-renin, hypertension. They are effective when used alone but are often administered with a thiazide diuretic, in which case the antihypertensive effects appear to be additive. The ACE inhibitors also relieve chronic congestive heart failure by reducing both preload and afterload.

Adverse effects: Proteinuria can occur, especially in patients with compromised renal function. The ACE inhibitors are contra indicated in patients with bilateral renal artery stenosis because acute renal failure may ensue. Cough and bronchospasm can occur. Hypotension has followed the first dose of the ACE inhibitors in Na⁺-depleted patients. Neutropenia can occur, and in patients who have impaired renal function or serious autoimmune disease (e.g. systemic lupus erythematosus), captoprilum should be used with caution. Neutropenia is rare with enalaprilum or lisinoprilum. Approximately 10% of patients treated with captoprilum develop reversible skin rashes, alterations in taste, proteinuria, and leucopenia. Headache, dizziness, and fatigue are the most common side effects associated with enalaprilum. Hyperkalemia has been reported.

Drugs which block receptors for angiotensin

Saralasinum, an angiotensin II₁ antagonist, exemplifies the drugs which interfere with the renin-angiotensin system by this mechanism. The drug can be given only by intravenous infusion. It is primarily used diagnostically to detect a renal cause of hypertension.

Antagonists of angiotensin II receptors

These drugs are divided in three groups according chemical structures.

1. Biphenyltetrazoles (losartanum, irberzartranum and other);
2. Nonbiphenyltetrazoles (eprozartranum, telmisartranum, candesartranum and others);
3. Nonheterocyclic compounds (valsartranum).

The compounds block effect of angiotensin II on receptors AT II (1) independently from ways of their synthesis. They decrease vessels peripheral resistance (afterload), cardiac venous return (preload), but have less adverse effects (cough, bronchospasm) than inhibitors of the ACE because do not influence synthesis of bradyckininum. They also increase effect of angiotensin II on the receptors angiotensin II (2) which stimulate regeneration, vasodilatation and other curative effects. Plasma renine activity also increases.

Losartanum (Cozaar) active metabolite is a long acting (6-8 hour) noncompetitive antagonist at the AT₁ receptor which contributes to the pharmacological effects of losartanum. Valsartanum (Diovan) has a higher affinity for the AT₁ receptor than losartanum, it does not have an active metabolite and has a slightly longer duration of action than losartanum. Irbesartanum (Avrovel) exhibits high bioavailability and high affinity for the AT II₁ receptor, it does not have an active metabolite and has a considerably longer duration of action than losartanum. Candesartranum cilexetil (Atacand) has an active metabolite with a long duration of action, is a prodrug and exhibits an AT II₁ receptor affinity 80 times that of losartanum. Telmisartanum (Micardis) is a longest-acting AT II₁ receptor antagonist and has no active metabolites.

Therapeutic use: Angiotensin II receptor antagonists are effective as monotherapy in the treatment of hypertension and of congestive heart failure in patients who do not tolerate the ACE inhibitors.

№	Drug	Drug forms
1.	Clophelinum	Tab. 0,000075, 0,00015; Amp. 0,01% - 1ml
2.	Methyldopha	Tab. 0,25
3.	Benzohexonium	Tab. 0,1, 0,25; Amp. 2,5% - 1ml
4.	Prazosinum	Tab. 0,001, 0,005
5.	Natrii	Amp. 0,05

	nitroprussidum	
6.	Magnesii Sulfas	Amp. 20%, 25% - 5, 10, 20ml
7.	Verapamilum	Tab. 0,04, 0,08; Amp. 0,25% - 2ml
8.	Nifedipinum	Tab. 0,01; Caps. 0,01, 0,02
9.	Amlodipinum	Tab. 0,005, 0,01
10.	Captoprylum (Capotenum)	Tab. 0,025, 0,05, 0,1
11.	Enalaprilum (Renitec)	Tab. 0,005, 0,01, 0,02
12.	Lisinoprilum	Tab. 0,005, 0,01, 0,02, 0,04
13.	Losartanum	Tab. 0,05
14.	Pentoxifyllinum	Tab. 0,4
15.	Dibazolum	Tab. 0,02; Amp. 0,5%, 1% - 1, 2, 5ml
16.	Papaverini hydrochloridum	Tab. 0,04; Amp. 2% - 2ml
17.	No-spanum	Tab. 0,04; Amp. 2% - 2ml

DRUGS USED IN THE TREATMENT OF HYPERLIPIDEMIA

Atherosclerosis is a primary cause of coronary heart diseases. Although development of coronary heart disease is determined by the interaction of numerous risk factors, the risk of coronary heart diseases is directly proportional to blood cholesterol levels. The cholesterol can be stored in hepatocytes as cholesterol esters, released in bile as cholesterol or as bile acids, used to form membranes or endogenous lipoproteins. **Drug therapy** is usually tried after dietary fat restriction, reduction of atherosclerosis risk factors, and moderate exercise programs have failed

to lower serum lipids to an acceptable level. Bile acid sequestrants, niacin, β -hydroxy- β -methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, and fibric acid derivatives demonstrably lower the risk of coronary artery disease; only niacin has been shown to reduce overall mortality.

Antihyperlipidemic agents

Cholestyraminum, cholestipolum: bile acid sequestrants

Mechanism of action and pharmacologic effects: Cholestyraminum and cholestipolum are resins which bind bile acids in the intestine, forming insoluble complexes, which are then excreted in the faeces. The loss of bile acids leads to an increased conversion of cholesterol into bile acids. There is also a compensatory increase in hepatic LDL receptors. The net effect is a reduction in serum LDL and cholesterol levels.

Therapeutic uses: The earliest use of bile acid sequestrants was to control pruritus in patients with cholestasis and elevated plasma bile acids. These agents are now also used to reduce elevated LDL levels. Patients with heterozygous familial hypercholesterolemia or polygenic hypercholesterolemia may be expected to respond.

Adverse effects: Since bile acid sequestrants are not absorbed, they have no adverse systemic effects. The most common untoward effects are gastrointestinal discomfort and constipation. The resins may cause or aggravate steatorrhea and may impede absorption of fat-soluble vitamins. These agents may bind other drugs (e.g. thiazides, anticoagulants, digitalis glycosides), impeding their absorption. Esetrolum blocks mechanisms of cholesteryne absorption.

HMG CoA reductase inhibitors: Lovastatin, simvastatinum, fluvastatinum, pravastatinum, atorvastatinum, rosuvastatinum

Mechanism of action and pharmacologic effects: 3-HMG CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis. Drugs which inhibit HMG CoA reductase are highly effective in lowering serum LDL-cholesterol levels. HMG CoA reductase inhibitors block the hepatic synthesis of cholesterol. This block leads to a compensatory reduction of serum LDL. There is also a compensatory increase in synthesis of HMG CoA reductase so that inhibition of cholesterol synthesis is not

complete. These drugs reduce serum levels of LDL, LDL-cholesterol, VLDL-cholesterol, and triglycerides. They elevate HDL-cholesterol. The decrease in LDL appears to result from an increase in hepatic LDL receptors, which causes an increase in receptor-mediated clearance of LDL and IDL.

Therapeutic uses: Statins are indicated in patients with hypercholesterolemia who are at high risk of myocardial infarction; for types IIa and IIb hyperlipoproteinemia in which LDL and total cholesterol are elevated; in secondary hyperlipoproteinemia due to diabetes mellitus or nephrotic syndrome; in patients with combined elevated cholesterol and triglycerides.

Adverse effects. Serum hepatic transaminases and muscle creatine phosphokinase (CPK) levels are elevated. Gastrointestinal reactions include flatulence and diarrhea. Periodic slit-lamp examinations are suggested before and during therapy, because ocular opacities have been noted in dogs. Myopathies, sometimes progressing to rhabdomyolysis and renal failure.

Niacin (nicotinic acid) has three special features as hypolipidemic drug: beneficial effects on serum lipoproteins, it is the least expensive and least tolerated.

Mechanism of action and pharmacologic effects. In large doses, niacin reduces serum triglycerides by lowering formation and secretion of the VLDL, usually within 1-4 days. The reduction of the VLDL in turn reduces the IDL and the LDL. Niacin usually produces a mild to moderate increase in the HDL. The VLDL-reducing action of niacin is independent of its vitamin activity. Hypolipidemic mechanism may involve inhibition of lipolysis in adipocytes, inhibition of hepatic triglyceride esterification, increased activity of lipoprotein lipase. Niacin does not significantly affect either total body production or biliary excretion of cholesterol.

Therapeutic uses: Niacin is helpful in controlling a wide range of hyperlipidemias. It is particularly useful for type V hyperlipoproteinemia, characterized by severe hypertriglyceridemia and elevated chylomicrons.

Adverse effects: Niacin produces prostaglandin-mediated intense flushing and itching. Gastrointestinal distress is common and peptic ulceration occurs. Hepatic dysfunction may occur with high-dose regimens. Glucose intolerance and

hyperuricemia may also occur.

Fibric acid derivatives: gemfibrozil, etofibratum, bezafibratum, fenofibratum, ciprofibratum

Mechanism of action and pharmacologic effects. The fibric acid derivatives lower serum VLDL levels, thus reducing serum triglycerides. With **fibric acid derivatives** the net effect on serum cholesterol in most patients is minimal. However, serum cholesterol is significantly reduced in patients with familial type III hyperlipoproteinemia. They lower plasma VLDL-cholesterol levels, lowers LDL-cholesterol to a lesser degree, and raises HDL-cholesterol.

Mechanism of action: All compounds stimulate receptors of activators of peroxysomes (PPARs), change expression of genes and activity of enzymes of lipid metabolism. Fibric acid derivatives increase the activity of lipoprotein lipase, the enzyme which degrades chylomicrons and the VLDL. They decrease hepatic synthesis and release of the VLDL, reduce the VLDL-HDL lipid exchange, causing increased HDL-cholesterol levels, increase hepatic clearance of the VLDL and IDL, causing lower LDL-cholesterol levels.

Therapeutic uses: Fibric acid derivatives are indicated for patients with familial type III hyperlipoproteinemia, in which the VLDL and IDL levels are increased. They are the first-choice drug for hypertriglyceridemia, whether or not accompanied by hypercholesterolemia. They are also useful in type V hyperlipoproteinemia in which both chylomicron and triglyceride levels are increased.

Adverse effects: The most common unwanted effects are mild gastrointestinal reactions. Some patients may show a paradoxical increase in LDL-cholesterol. Myositis with elevated CPK and serum glutamic oxaloacetic transaminase (SGOT) levels can occur, risk of myopathies, rhabdomyolysis. The fibric acid derivatives increase the incidence of cholelithiasis and cholecystitis, gallstone risk, erectile dysfunction. Cardiac arrhythmias have been reported. Clofibratum displaces warfarinum from albumin, potentiating its anticoagulant effects.

Probucolum - lipophilic antioxidant

Mechanism of action and pharmacologic effects: Probucolum reduces total serum cholesterol; it lowers HDL-cholesterol more than LDL-cholesterol; has little or no effect on the VLDL or triglycerides. The mechanism of action is to involve: synthesis of cholesterol-poor HDL; inhibition of early stages of cholesterol synthesis; an increased rate of the LDL degradation. Probucolum inhibits the oxidation of the LDL, thereby preventing its uptake by macrophages.

Therapeutic uses: Probucolum is generally combined with another type of lipid-lowering drug for the treatment of general hypercholesterolemia.

Adverse effects: Gastrointestinal reactions are the most common untoward effects. Prolongation of the Q-T interval has been reported. There are angioprotectors which normalize vessel wall metabolism – **calcii dobesilas** and **quercetinum** are attributed to this group.

Angioprotectors (endothelium-tropic agents) decrease the permeability of endothelium to atherogenous lipoproteins. **Parmidinum** is indicated in atherosclerosis of cerebral, coronary and peripheral blood vessels, diabetic angiopathy, thrombosis of veins in the retina, endarteritis obliterans and trophic ulcers of the lower extremities. It is the most effective in the affection of peripheral vessels. The antioxidants also have angioprotective action.

Besides specific hypolipidemic drugs and angioprotectors the complex pharmacotherapy of atherosclerosis also includes lipotropic drugs: **lipostabilum**, **lipoic acid**, **lipamidum**, **methioninum** and others. These drugs stimulate formation of phospholipids which activate destruction of cholesterol, increase stability of protein-lipid complexes, improve rheologic properties of blood and prevent fatty degeneration of the liver.

Nº	Drug	Drug forms
1.	Phenofibratum	Caps. 0,1
2.	Simvastatinum	Tab. 0,005, 0,01, 0,02, 0,04
3.	Lovastatinum	Tab. 0,1, 0,2, 0,4
4.	Calcii dobesilas	Tab. 0,25
5.	Quercetinum	Tab. 0,02

DIURETIC AGENTS

Diuretics are drugs which promote a net loss of sodium ions (Na^+) and water from the body, the net result being an increase in urine flow. Some drugs can increase urine flow by non renal mechanisms (e.g. by increasing cardiac output in a patient with congestive heart failure), but these drugs are not generally regarded as diuretics.

Diuretics can be classified by structure and mechanism of action into eight groups listed below.

1. Diuretics directly influence the epithelium of renal tubules:

1.1. On apical membrane – Potassium (K^+)-sparing diuretics;

1.1.1. Antagonists of aldosteronum – Spironolactonum, Eplerenonum;

1.1.2. Concurents for transport of Na^+ - Triamterenum, Amiloridum;

1.2. On distal membrane;

1.2.1. Inhibitor carbonic anhydrase – Diacarbum;

1.2.2. Thiazide diuretics – Hydrochlorthiazidum (Dichlothiazidum), Cyclomethiazidum;

1.2.3. Thiazide – like diuretics – Clopamidum, Chlortalidonum, Indapamidum;

1.2.4. High ceiling (loop) diuretics – Furosemidum, Torasemidum, Acidum etacrynicum, Bumetanidum;

2. Osmotic diuretics – Mannitum, Urea pura;

3. Drugs that increase circulation – Euphyllinum, Teophyllum;

4. Herbs – Folium Ortosiphoni, Herba Equiseti arvensi, Folium Uvae Ursi;

Although an individual diuretic can action several areas of the nephron, the major sites of action for the diuretics may be summarized as follows:

1. Those acting on the proximal tubules mainly:

a. Osmotic diuretics;

b. Xanthine diuretics;

c. Carbonic anhydrase inhibitors;

d. Acidifying salts.

2. Those acting on the ascending limb of the loop of Henle:

High-ceiling (loop) diuretics.

3. Those acting on the distal tubule:

Thiazide diuretics and thiazide like diuretics.

4. Those acting on the collecting tubules K^+ sparing diuretics.

High ceiling (loop) diuretics, osmotic diuretics have quick action. Antagonists of aldosterone have slow action. Other diuretics have moderately quick action. Diuretics are frequently employed for the clinical management of disorders involving abnormal fluid distribution, such as edema, or for hypertension. They are also used to reduce the toxicity of ingested or administered substances. For example, mannitol, an osmotic diuretic, reduces the renal toxicity of the antitumor agent cisplatin, and acetazolamide, a carbonic anhydrase inhibitor, is used to alkalinize the urine and increase salicylate elimination. The efficacy of the different classes of diuretics varies significantly with the xanthine diuretics being the least effective and the "high-ceiling," or "loop," diuretics being the most effective. The establishment of a net negative Na^+ balance, particularly with the less efficacious diuretics, can also depend upon limiting the Na^+ intake.

Carbonic anhydrase inhibitors

Mechanism of action: Diacarbam inhibits the carbonic anhydrase enzyme predominantly at the proximal convoluted tubules, causing a reduction in hydrogen ions for $Na^+ - H^+$ exchange. Carbon dioxide (CO_2) reabsorption from the glomerular filtrate is suppressed, and HCO_3^- -excretion is increased. Due to decreased Na^+ reabsorption, the $Na^+ - K^+$ exchange in the distal convoluted tubule increases, causing a loss of K^+ in the urine. To maintain ionic balance, Cl^- is retained by the kidney, resulting in a hyperchloremic acidosis. Increased urinary amounts of Na^+ , K^+ , and HCO_3^- result in an alkaline urine. Diacarbam may decrease intraocular pressure.

Therapeutic uses: Diacarbam is used in glaucoma for reducing the rate of aqueous humor formation, as helping agent in petit mal epilepsy, to decrease the rate of spinal fluid formation.

Adverse effects are: blood dyscrasias and allergic skin reactions, drowsiness and paresthesias, inhibition iodide uptake.

Thiazide diuretics (benzothiadiazides) and thiazide like diuretics

Mechanism of action: The thiazide diuretics – dichlothiazidum (Hydrochlorothiazidum) vary widely in their potency of carbonic anhydrase inhibition. Structurally these drugs have a sulfonamyl group, which accounts for their inhibition of carbonic anhydrase activity. They inhibit energetic metabolism – Na-K-ATPase activities, adenylatcyclase, they inhibit Cl⁻ reabsorption, particularly in the distal portion of the ascending limb of Henle's loop and the very early portion of the distal tubule. There is an increased renal excretion of Na⁺, Cl⁻, HCO₃⁻, and K⁺, keep Ca²⁺.

Hypotensive effect of the thiazide diuretics is a result of a reduction in blood volume, direct relaxation of arteriolar smooth muscle, decrease of its sensitivity to noradrenaline influence. Dichlothiazidum decreases intraocular pressure. Certain other thiazidelike sulfonamide diuretics – indapamidum, clopamidum, chlorthalidonum, quinethazonum, and metolazonum are pharmacologically similar to the thiazides, but act longer because they also influence proximal tubules.

Hydrochlorothiazide given orally 1-2 times a day. Cyclomethiazidum given orally 1 time a day.

Therapeutic uses: Thiazide diuretics are used to treat chronic edema, usually associated with cardiac decompensation. A diuretic response occurs in 2-3 hours and lasts for about a day. Thiazides are used in the treatment of essential hypertension. They sometimes are effective in the treatment of nephrosis. They are occasionally used for the palliation of nephrogenic and pituitary - antidiuretic hormone (ADH)-sensitive - diabetes insipidus. By decreasing the urinary volume through their natriuretic action, these drugs may enhance the action of the ADH. They are used in the management of hypercalciuria.

Adverse effects: Electrolyte abnormalities such as hypokalemia may occur. Thus, K⁺ supplementation is recommended. Particular caution is needed when a thiazide is administered in combination with a digitalis preparation for the treatment of congestive heart failure. If digitalis is administered in the presence of hypokalemia, digitalis intoxication and serious cardiac arrhythmias can result.

Hyperuricemia may result from an inhibition of renal tubular secretion of uric acid. Since thiazides are excreted by glomerular filtration and tubular secretion, the thiazides compete with uric acid for tubular secretion. Hyperglycemia can occur, aggravating preexisting diabetes mellitus. Thiazides may interfere with the conversion of proinsulin to insulin. Thiazide diuretics may reduce urinary calcium excretion. Hypercalcemia and hypophosphatemia may be occurred. Suppression of parathyroid hormone and reduction in intestinal calcium absorption may also occur. Thiazide diuretics occasionally may aggravate renal or hepatic insufficiency. Lassitude, weakness, and vertigo may occur with large doses. Rarely thiazide-induced pancreatitis, elevating lipid and lipoprotein changes may occur.

High-ceiling (loop) diuretics: furosemidum, torasemidum, acidum ethacrynicum.

Mechanism of action: These diuretics inhibit electrolyte reabsorption in the thick ascending limb of the loop of Henle (Na^+ , K^+ , Cl^- , Mg^{2+} , Ca^{2+} , PO_4^{3-} , HCO_3^-) and also acidum etacrynicum bromidum. They inhibit energetic metabolism and may interact with Na^+ and Cl^- channels. Cl^- -excretion is greater than Na^+ excretion. These diuretics increase renal blood flow without increasing the glomerular filtration rate. Large doses promote uric acid excretion. Hypochloremic alkalosis may occur, but it does not produce a refractory state. Furosemidum, a structural derivative of the thiazides, and bumetanidum are weak inhibitors of carbonic anhydrase, probably as a result of the diuretics substituted sulfonamide side chain. Torasemidum excrete K^+ less. Acidum etacrynicum lacks of a sulfonamyl group and does not inhibit carbonic anhydrase, but inhibit antidiuretic hormone. The drugs decrease arterial pressure, pre- and postload on heart.

Furosemidum, torasemidum and bumetanidum, acidum etacrynicum are administered orally, intramuscularly or (more frequently) intravenously. One of the main differences between furosemidum and acidum etacrynicum is that the former has a broader dose-response curve.

Therapeutic uses: The high-ceiling diuretics are the most effective diuretic agents available. They are useful for the treatment of acute episodes of pulmonary

edema. Edema associated with congestive heart failure, cirrhosis, and renal disease. Because of its potent edema-reducing ability, furosemidum has been used to treat elevated intracranial pressure.

Adverse effects: Fluid and electrolyte imbalances are the most commonly seen adverse effects. The high-ceiling diuretics frequently are administered to patients on digitalis so hypokalemia may be a particular problem. Hyperuricemia results because these diuretics are actively secreted by the renal and biliary secretory systems, and thus, they block (by competition) renal uric acid secretion. While hyperuricemia is relatively common, it is benign. The drugs make worse lymph circulation in ears. Transient deafness is a risk if a potentially ototoxic drug (e.g. an aminoglycoside antibiotic) is administered concomitantly in such circumstances, another class of diuretic should be employed. Transient granulocytopenia and thrombocytopenia occur. Severe muscle pain and tenderness seldom occur.

Osmotic diuretics: mannitolum, urea pura

Mannitolum and urea pura owe their effects to the physical retention of fluid within the nephron rather than to direct action on cellular sodium transport.

Mechanism of action: Osmotic diuretics are filtered at the glomerulus but are poorly reabsorbed due to their molecular size. The presence of these unresorbed solutes in the proximal tubule causes decreased reabsorption of Na^+ and water, resulting in a large volume of urine. Mannitolum causes an increase in renal medullary blood flow via a prostaglandin-mediated mechanism. Osmotic diuretics do not markedly influence Na^+ and Cl^- excretion.

Mannitolum and urea are administered intravenously.

Therapeutic uses: The osmotic diuretics are used to reduce cerebrospinal fluid pressure. They will transiently reduce intraocular fluid pressure in glaucoma. They have also served as an adjunct in the prevention or treatment of oliguria and anuria. The osmotic diuretics, especially mannitolum, are employed prophylactically for acute renal failure in situations such as cardiovascular operations, treatment with nephrotoxic anticancer agents, severe traumatic injury, and management of hemolytic transfusion reactions. Mannitolum is used to promote the elimination of injected toxic

substances.

Adverse effects are the following: headache, nausea, vomiting, chest pain. Because they do not penetrate cells and their mode of excretion is by glomerular filtration, osmotic diuretics increase blood volume, which can cause decompensation in patients with congestive heart failure. When osmotic diuretics are used for the treatment of renal failure or cirrhotic disease, hyperosmolality and hyponatremia can occur.

Potassium (K^+)-sparing diuretics : triamterenum and amiloridum

Mechanism of action: Triamterenum and amiloridum inhibit active Na^+ reabsorption, because their physical and chemical characteristics are similar to hydrotating natrium in cortical collective duct. They influence distal Na^+ and K^+ transport. This reduces the net driving force for K^+ secretion. Triamterenum and amiloridum cause a moderate increase in Na^+ , Cl^- and HCO_3^- -excretion. Their action is independent of aldosterone. Triamterenum is administered orally twice daily. Amiloridum is administered orally once daily.

Therapeutic uses: Triamterenum or amiloridum are used in combination with other diuretic agents for the treatment of hypertension; this combined therapy augments the natriuretic effect while diminishing kaliuresis.

Adverse effects: Hyperkalemia may occur; thus, K^+ -sparing diuretics are not given in combination with one another and are contraindicated in hyperkalemic patients. Hyperkalemia is especially likely in diabetics or in those with impaired renal function. Reversible azotemia is relatively common. Gastrointestinal disturbances, including nausea and vomiting, occur on occasion. Leg cramps may occur. Dizziness has been reported.

Spironolactonum (Aldactonum), eplerenonum (Inspra) - competitive antagonist of the mineralocorticoid, aldosteronum.

Mechanism of action: They interfere with the aldosterone-mediated $Na^+ - K^+$ exchange, increasing Na^+ loss at the distal tubular site while decreasing K^+ loss.

Therapeutic uses: Spironolactonum, eplerenonum are often used as an adjunct to other diuretics to reduce the loss of K^+ in the management of refractory edema,

such as that associated with Laennec's cirrhosis. They are also used when adrenal gland tumors result in increased aldosterone levels. They can be used for edema due to congestive heart failure, although other diuretic agents are more effective. Eperenonum is more active than spironolactonum.

Adverse effects: Hyperkalemia may occur or be exacerbated, especially in patients with impaired renal function. Spironolactonum, eplerenonum are contraindicated in patients with acute renal insufficiency or hyperkalemia and are not given in combination with another K^+ -sparing diuretic. Gastrointestinal disturbances include diarrhea. Androgenic side effects include menstrual irregularities and hirsutism. The CNS disturbances include lethargy.

Nº	Drug	Drug forms
1.	Dichlothiazidum	Tab. 0,1, 0,025
2.	Klopamidum (Brinaldix)	Tab. 0,02
3.	Furosemidum	Tab. 0,04; Amp. 1% 2ml
4.	Acidum etacrynicum	Tab. 0,05, 0,1; Amp. 0,05
5.	Spironolactonum	Tab. 0,025
6.	Triamterenum	Pulv., caps. 0,05
7.	Mannitum	Flac. 15% - 200, 400, 500ml; Flac. 30,0

DRUGS USED IN THE TREATMENT OF GOUT

Gout is the most readily treated of all the rheumatic disorders. Hyperuricemia is not always accompanied or followed by gout, but when gout occurs, it is preceded by hyperuricemia. Excessive uric acid synthesis associated with myeloproliferative disorders and malignancies, especially after antineoplastic or radiation therapy (conditions which lead to high rates of cell formation and destruction will lead to increased serum levels of purines, derived from cellular nucleic acids, and will, thus,

result in hyperuricemia).

Drugs using in gout are divided:

I. Drugs used in acute attack (non steroidal inflammatory medicaments).

II. Drugs for treatment of gout.

1. Uricodepressive drug (allopurinolum);

2. Uricosuric drugs;

2.1. Drugs inhibiting reabsorption of uric acid (aethamidum, benzbromuronum, probenecidum, sulphitratonum);

2.2. Drugs improving uratesolubility (urodanum);

2.3. Drugs loosening concrements (Fitolysinum, Urolesanum, Herba Polygoni avicularis, Rubia tinctorum siccum).

Probenecidum

At therapeutic doses, probenecid lowers serum levels of uric acid by inhibiting the proximal tubular reabsorption of uric acid. In low doses, probenecidum blocks the tubular secretion of uric acid, while at therapeutic doses probenecidum is uricosuric. As a general inhibitor of the tubular secretion of organic acids, probenecidum will also increase serum levels of other organic acids, such as penicillinum. Probenecidum has no analgesic activity.

Therapeutic uses: By virtue of its uricosuric effects probenecidum is useful for the treatment of chronic gout.

Adverse effects: The most common adverse effects being gastrointestinal disturbances and hypersensitivity reactions, such as skin rash and drug fever.

Sulfinpyrazonum

Sulfinpyrazonum is a sulfoxide derivative of phenylbutazonum. Sulfinpyrazonum inhibits the proximal tubular reabsorption of uric acid. A hydroxy metabolite is also a potent uricosuric substance. Sulfinpyrazonum also inhibits prostaglandin synthesis and interferes with a number of platelet functions, including adherence to subendothelial cells.

Therapeutic uses: Sulfinpyrazonum is used for the treatment of chronic gout, it is being examined as an antithrombotic agent.

Adverse effects are similar to those seen with probenecidum.

Colchaminum - this alkaloid derivative is effective in the treatment of acute attacks of gout and is also effective if given prophylactically to prevent such attacks. Colchaminum inhibits the migration of polymorphonuclear leukocytes to the inflammatory area. It is proposed that Colchaminum produces ultrastructural alterations in leukocytes by attaching to the microtubular protein (tubulin) that is involved in cell motility and, thus, prevents the migration of granulocytes and inhibits phagocytic activity. Colchaminum also blocks cell division by binding to mitotic spindles (mitotic blockade).

Adverse effects: Nausea, vomiting, and abdominal pain with diarrhea are warning signs that more serious toxicity could result and may indicate the need to discontinue colchicine therapy. The most serious untoward effects which occur with chronic administration are agranulocytosis, aplastic anemia, myopathy, and alopecia.

Allopurinolum is an isomer of hypoxanthine, a purine. Allopurinolum, together with its primary metabolite alloxanthine, prevents the terminal steps in uric acid synthesis by inhibiting the enzyme xanthine oxidase, which converts xanthine or hypoxanthine to uric acid. Hyperuricemia is, thus, reversed by the blockade of uric acid production. Allopurinolum acts as a competitive inhibitor, while alloxanthine acts noncompetitively. The inhibition of xanthine oxidase causes serum levels of the catabolic intermediates xanthine and hypoxanthine to increase. Renal clearance of these substances, however, is rapid and their increased plasma concentrations do not exceed their solubility. Thus, crystallization within joint tissue does not occur as it would with comparable levels of uric acid.

Adverse effects: Allopurinolum is well tolerated. The most common untoward effects are hypersensitivity reactions, including cutaneous reactions.

Acute attacks of gout occur more frequently during initial therapy with allopurinolum. This may be due in part to the active dissolution of microcrystalline deposits of sodium urate (tophi) within subcutaneous tissue, resulting in transient periods of hyperuricemia and crystal deposition in joint tissue. To reduce this complication, simultaneous prophylactic therapy with colchaminum is indicated.

Nonsteroidal anti-inflammatory agents are used in the treatment of gout

Aethamidum promotes excretion of urates. It is used in case of gout, chronic polyarthritis, blocks the active reabsorption of uric acid in the proximal tubules following its glomerular filtration. **Indications:** chronic gout. **Adverse effects** are connected with nausea, vomiting, pain in epigastrium.

Urodanum is a combine drug, components of which bind to urates, creating water-soluble complexes that leads to increase of their excretion from the organism. It changes pH and melts urates.

№	Drug	Drug forms
1.	Allopurinolum	Tab. 0.1
2.	Aethamidum	Tab. 0.35
3.	Uropodanum	Flac. 100
4.	Urolesanum	Flac. 15 ml
5.	Herba Polygoni avicularis	Infusum 1:10

DRUGS WHICH INFLUENCE UPON THE MYOMETRIUM

The contractile activity and tone of myometrium are regulated by neurohumoral mechanisms. The myometrium contains M-cholinoceptors, α - and β_2 -adrenoceptors. The stimulation of M-cholinoceptors and α -adrenoceptors leads to stimulation of the myometrium tone and contractions, and the excitation β_2 -adrenoceptors causes its relaxation. In addition to this there are some biologically active substances which exert significant stimulating influence upon the myometrium contractile ability. They are female gonadal hormones — estrogens, posterior pituitary hormone — oxytocin, some prostaglandins. There are also some endogenous substances which inhibit the myometrium contractile ability (for example, progesterone).

The pharmacological regulation of the contractile function of the myometrium is based on the use of the endogenous substances which regulate the myometrium activity or on the use of the drugs which exert influence upon the neurohumoral regulation of the myometrium tone and contractile ability.

Drugs which influence upon the tone and contractile ability the myometrium are divided into the following groups:

I. Drugs which exert influence upon the myometrium rhythmical contractile activity:

1. Drugs which stimulate the myometrium rhythmical contractile activity and relaxing the uterus cervix – *dinoprost* (prostaglandin F_{2α}), *dinoprostone* (prostaglandin E₂);

2. Drugs which in low doses stimulate the uterine rhythmical contractile activity and in high doses increase the myometrium tone: *pituintrinum, oxytocinum*;

3. Drugs which increase the uterine rhythmical contractile activity: *pachycarpine, spherophysine, sygethin, castor oil*;

4. Drugs which decrease the uterine contractile ability: a) β₂-adrenomimetics - *fenoterol, salbutamot*, b) general anesthetics – natrii oxybutyras; c) miscellaneous drugs – *magnesium sulfate, tocopherol, progesterone*.

II. Drugs which increase the myometrium tone:

1. Drugs of plant origin (ergot alkaloids) - *ergot extract, ergotal, Ergotamine, ergometrine, methylegometrine*;

2. Synthetic drugs – *cotarnine*.

III. Drugs which decrease the cervix tone - *atropine, papaverine, drotaverine*.

The prostaglandins (dinoprost, dinoprostone) exert significant stimulating influence upon the myometrium. They cause the rhythmical uterine contractions and the relaxation of the uterus cervix. These drugs act upon the myometrium independently on the presence and term of pregnancy. The action upon the cervix is caused by direct stimulation of the enzyme "collagenase" which breaks down the collagen network, that results in softening of the cervix. These drugs are used for medical abortions and less commonly - for the stimulation of labor. The side-effects of dinoprost are the increase of the bronchial smooth muscle tone, constriction of pulmonary blood vessels, strengthening of myocardial contractions, increase of the heart rate, that may lead to the arterial hypertension. Dinoprostone, on the contrary, dilates the pulmonary vessels and bronchi. It is also able to decrease the blood

pressure and to cause reflex tachycardia. Both drugs can cause nausea, vomiting, headache, transitory elevation of the body temperature. They are introduced by intravenous way or directly into the cervix.

Oxytocin is an octapeptide secreted by the posterior pituitary. In pharmacological doses it is used to induce uterine contractions and to maintain labor, in high doses it causes strong single uterine contraction. The mechanism of its action is alteration of transmembrane ionic currents in myometrial smooth muscle cells, that leads to the development of sustained uterine contractions. The sensitivity of the uterus to oxytocin increases during pregnancy. Oxytocin also causes the contraction of myoepithelial cells surrounding mammary alveoli, which leads to milk ejection. Oxytocin has weak antidiuretic and vasopressor activity. It is used for induction or stimulation of the labour and for augmentation of the dysfunctional labor, for arresting of atonic uterine hemorrhages, in uterine subinvolution in the postnatal period. The side-effects are hypertension, uterine rupture, fetal death. There is a synthetic oxytocin derivative – *desaminoxytocinum* (demoxytocin). It has higher activity and is used by buccal or sublingual ways. The main application for its use is uterine subinvolution in the postnatal period.

Pituitrinum is an aqueous extract of the cattle posterior pituitary. It contains both oxytocin and vasopressin (antidiuretic hormone, ADH). In consequence of the presence of vasopressin it increases the arterial pressure. The applications of its use are similar to the ones of oxytocin. It is introduced by subcutaneous and intramuscular ways.

Pachycarpine and spherophysine belong to ganglioblocking drugs. Their ganglioblocking activity is low and short. These drugs also exert stimulating influence upon the myometrium, that is why they are sometimes used for the stimulation of labor. Sygethin increases the myometrium contractile activity and improves the placental blood circulation. It is used for the stimulation of labour and for the prophylactics of the fetus hypoxia. Castor oil belongs to laxative agents. Due to irritation of the intestinal mucosa it causes the reflex increase of the intestinal peristalsis and the uterine contractile ability.

β_2 -adrenomimetics decrease the uterine tone owing to the excitation of β_2 -adrenoceptors located in the myometrium, which results in myometrium relaxation. It is supposed that the mechanism of their action is inhibition of the phosphorylation of myosine. They are indicated mainly for the delay of the premature labor. Their efficiency is high, but they do not exert selective action upon the myometrium. In addition to the uterus relaxation they cause side-effects associated with the excitation of β_2 -adrenoceptors of other localization and of β_1 -adrenoceptors. Natrii oxybutiras provides the decrease of myometrium tone due to the inhibition of central regulation of the process of labor. Magnesium sulfate decreases the myometrium contractile ability due to the blockade of calcium channels and to the reduction of calcium influx into the cytoplasm of the myometrium cells. It also exerts direct spasmolytic action. These drugs are indicated in the threat of abortion.

Drugs which increase the myometrium tone include ergot alkaloids and cotarnine. They are used mainly for the arresting of uterine atonic hemorrhages. The principle of their action is stable increase of the myometrium tone, which leads to the mechanical compression of small uterine vessels. The side-effects of these drugs are nausea, vomiting, diarrhea, headache. The overdosage of ergot alkaloids is manifested in motor excitement, convulsions, vomiting, diarrhea, pain in the epigastric area, tachycardia, disorders of sensibility.

Drugs which decrease the cervix tone include M-cholinolytics (atropine) and myotropic spasmolytics (papaverine, drotaverine). The mechanism of M-cholinolytic action is the blockade of M-cholinoceptors located in the uterus cervix, which leads to the relaxation of its smooth muscles. The myotropic spasmolytics exert direct relaxing action upon the cervix smooth muscles. These drugs are used in labour for the increase of cervix dilation.

№	Drug	Drug forms
1.	Ergometrini Maleas	Tab. 0.0002 Amp. 0.02% - 1, 0.5 ml
2.	Oxytocinum	Amp. 1 ml (5UA)

3.	Pituitrini pro Injectionibus	Amp. 1 ml (5UA)
4.	Dinoprost (Prostaglandinum F _{2α})	Amp. 0.005; 0.001
5.	Atropini Sulfas	Tab. 0.0005 Amp. 0.1% 1 ml
6.	Partusisten Fenoterolum	Tab. 0.005 Amp. 0.005% 10 ml

Drugs used in Gastrointestinal disorders

Drugs stimulating appetite are amara tinctura Absinthii, plantaglicidum, and others which irritate mouth mucosa receptors.

Anorexigenic drugs include as main central serotonin agonist sibutramidum (meridia) which oppresses hunger centre and peripheral drug orlistatum (xenicalum) inhibiting lipase. Other drugs which inhibit hunger center: a) inhibit catecholamine system – phepranonum, desopimonum, and mazindolum; b) inhibit serotonine system – phenphluraminum.

Drugs which increase gastrointestinal motility

Decreased gastrointestinal motility can be result of a systemic disease, intrinsic gastrointestinal disorders or medication.

These drugs are classified as:

1. M-Cholinomimetic drugs – aceclidinum;
2. Anticholinesterase drugs – proserinum, pyridostigmini bromidum, and distigmini bromidum;
3. Prokinetics – metoclopramidum (cerucalum), cisapridum (propulsid), and tegaserodum (Zelnorm).

Metoclopramidum is central dopamine antagonist resulting in increased gastric contraction, enhanced gastric emptying and small lower transit, cause antiemetic effect. Peripherally it stimulates the release of intrinsic postganglionic

stores of acetylcholine and sensitizes the gastric smooth muscle to muscarinic stimulation. It can decrease the acid reflux into the esophagus.

Therapeutic uses: Metoclopramidum is used in patients with diabetic, postoperative idiopathic gastroparesis, in lower esophagus sphincter pressure, as antiemetic drug.

Adverse effects are fatigue, insomnia, after motor coordination, Parkinsonian side effects, acute dystonic reactions.

Cisapridum and **teguserodum** are serotonin-4 (5HT₄) receptor agonist, facilitate the release of acetylcholine.

Cathartics stimulate afferent nerves to initiate a reflex increase in gut motility. **Plant cathartics** are divided into **oils** (oleum Ricini) and the drugs consisting of **anthraquinone derivatives**.

Oils. Oleum Ricini is a bean oil which is hydrolyzed in the gut to ricinoleic acid and glicerinum. The ricinoleic acid acts on the ileum and colon to induce an increased fluid secretion and colonic contraction. It is used in acute obstipation.

Anthraquinone derivatives (drugs of senna, rhei, aloe etc). They biotransform to emetinum and acidum chrisophanicum which irritate receptors of colon rather than on the ileum, produce evacuation in 8-10 hours. The main drugs are senadexinum, fun sena. Synthetic drugs - isapheninum, bisacodylum, natrii picosulfas (guttalax), also irritate colon receptors and are used as antaquinone derivatives in chronic obstipation.

Osmotic catharths (magnesii sulfas) increase Lumen osmolarity, irritate intestine receptors. They are used in intoxication. Osmotic laxatives (e.g. lactulose, sorbitolum are purely absorbed, and draw additional fluid into gastrointestinal tract, increase lumen osmolarity. Oleum Vasselini, Oleum Amygdalarum are stool softeners. Methylcellulosa, laminaridum are bulk-forming laxatives.

Drugs that decrease gastrointestinal motility are divided into:

1. M-Cholinoblockers: atropine sulfas, platyphyllini hydrotartras, and methacinum;
2. Spasmolytics: papaverini hydrochloridum, no-spanum, mibeverinum;

3. Drugs for treating diarrhea;

3.1. Agonists opioid receptors – loperamidum, domperidonum;

3.2. Silicate drugs – enterosgelum, silix; smekta, kaopectate;

3.3. Microbial drugs;

3.3.1. Lactobacteries – lactobacterium;

3.3.2. Sugar-microbes – enterolum;

3.3.3. Probiotics – chylack, linex;

3.3.4. Others – coly-bacterinum, lactobacterinum, biosporinum etc.

Loperamidum is an agonist of the opioid receptor. It protects against diarrhea, reduces the daily fecal volume, decreases intestinal fluid and electrolyte loss.

Adverse effects: Abdominal pain, distention, constipation, dry mouth, hypersensitivity, nausea, vomiting, dizziness.

Emetic drugs are divided into:

1. Drugs of central action – apomorphini hydrochloridum acting on the hemoreceptor trigger zone connecting to the emetic centre through the fasciculus solitarius;

2. Drugs of the peripheral action;

2.1. Expectorantive plant drugs of Thermopsisidis, Ipecacuanhae;

2.2. Solutio Ammonii causticum.

Antiemetics are classified into:

1. Antihistamines – diprazinum (pipolfenum);

2. Dopamine receptor blockers – metoclopramidum (cerucal), domperidonum (motilium), thiethylperatinum (forecanum);

3. Anticholinergics - scopolamini hydrobromidi (Aeronum);

4. 5-HT₃ receptor agonists – ondansetronum (Zofranum), granisetronum (Kytrilum), tropisetronum (Novobanum);

Drugs increasing stomach secretion. These group of drugs is divided into:

1. Diagnostic drugs – pentagastrinum;

2. Drugs of replacing therapy – acidum hydrochloricum dilutum, pepsinum, succus gastricus naturalis that indicate in hypoacidic, anacidic gastritis, achylia.

Polyenzyme drugs such as Pancreatinum, Festalum, Panzinorm forte, Mezym forte are used when secretion of stomach glands, pancreas, bile secretion are diminished.

Drugs that decrease gastric acid secretion are divided into:

1. M-Cholinoblockers;
 - 1.1 Nonselective drugs: atropini sulfas, platyphyllini hydrotartras, and methacinum;
 - 1.2 Selective M₁-Cholinoblockers: pirenzepinum (gastrocepinum);
2. H₂-histamine receptor antagonists: ranitidinum (zantac), famotidinum (quamatelum), nizatidinum (axid), and roxatidinum;
3. Proton pump inhibitors: omeprazolum (Losec, Omez), lansoprazolum (Lancerol), pantoprazolum (Controlock), rabeprazolum (Pariet), esomoprazolum (Nexium);
4. Antacides: magnesii oxydum, natrii hydrocarbonas, Almagel, Maalox, Alumini hydroxidum, Rennie etc.

H₂ receptor antagonists

The principal effect of H₂ receptor antagonists is to inhibit histamine-stimulated gastric acid secretion. They also inhibit gastric acid secretion induced by gastrin and acetylcholine.

Therapeutic uses: The major therapeutic use of H₂ receptor agonists is in the treatment of patients with duodenal and gastric ulcers and gastric hypersecretory states. The first drug was cimetidinum that is not used now because of adverse effects: some degree of renal dysfunction, that resulted in the CNS disturbances (e.g. confusion), antiandrogenic effect, resulting in gynecomastia in men and galactorrhea in women, reduces liver blood flow and, thus, can markedly decrease the hepatic clearance of drugs whose metabolism is dependent on liver blood flow (e.g. propranololum). Because cimetidinum reversibly inhibited the cytochrome P-450 hepatic enzyme system, a number of drug interactions are observed.

Ranitidinum is 4-12 times more potent than cimetidinum, and it is approved for the treatment of patients with gastroesophageal reflux disease. Ranitidinum does not

significantly affect the cytochrome P-450 hepatic enzyme system, but it does reduce liver blood flow, have adverse CNS effects and drug interactions. The risk of untoward antiandrogenic effects from ranitidine use appears to be minimal.

Famotidine is most potent on a weight basis. Its efficacy in patients with peptic ulcer disease is similar to that of other agents. Famotidine has a longer half-life than cimetidine or ranitidine (3 hours versus 2 hours). Pharmacodynamics and adverse reactions are similar to those of ranitidine.

Nizatidine has the highest bioavailability and shortest half-life (1.6 hours) of the currently available H₂-receptor antagonists. Nizatidine, like all of the currently available H₂-receptor antagonists, is principally excreted in the urine. Renal elimination involves both glomerular filtration and tubular secretion. Pharmacodynamics and adverse reactions are similar to those of ranitidine.

H⁺,K⁺-ATPase inhibitors.

Omeprazole is the prototype of the benzimidazole sulfoxide prodrugs that diffuse across the gastric parietal cell cytoplasm, where they are protonated. It binds to parietal cell H⁺, K⁺-ATPase, inhibiting secretion of hydrogen ions into the gastric lumen.

1. Omeprazole is unstable in acid and is formulated in gelatin capsules. It is metabolized in the liver and excreted in the bile and urine.

2. By irreversibly inhibiting parietal cell H⁺, K⁺-ATPase and preventing the secretion of hydrogen ions into the gastric lumen, the drug appears to be more effective than ranitidine for treatment of patients with gastroesophageal reflux. It has antihelicobacter effect.

3. Omeprazole inhibits the oxidative metabolism of phenytoin, diazepam, and other drugs.

4. Although the incidence of adverse effects is low, toxicologic studies using high doses of omeprazole have demonstrated gastric carcinoid tumors in rats. Intense acid suppression leads to increased gastrin secretion, which has a trophic effect on gastric mucosa.

Other proton pump inhibitors have the same pharmacodynamics.

Rabeprazolium is the most effective. Esomeprazolium, isomer of Omeprazolium, has better pharmacokinetics.

Antacides interact with the HCL. Some of them are absorbed: **magnesii oxidum, natrii hydrocarbonas, calcii carbonas, and magnesii trisilicus**. Natrii hydrocarbonas can cause systemic alkalization, sodium overload formation of heart increasing secretion. Calcium carbonas may induce hypercalcemia and reload increase of gastric secretions. Magnesii oxydum and magnesii hydroxydum may produce osmotic diarrhea and excessive absorption of magnesium in patients with renal failure may result in the CNS toxicity. Aluminii hydroxidum is association with constipation. **Almagel, Maalox** and aluminii hydroxidum are not absorbed.

Agents that reduce gastric acidity (gastroprotectors)

Gastroprotectors are drugs increasing gastric and duodenal mucose stability to aggressive factors of succus gastricus influence, they are divided:

1. Drugs increases mucosa defence function - Misoprostolum (Saiotec), Carbenoxolum, Enprostilum. Misoprostolum is a synthetic analogue of prostaglandinum E₁, stimulate mucose, bicarbonates secretion, decreases HCL secretion. Enprostilum is a synthetic analogue of prostaglandinum E₂. Carbenoxolum is a drug of acidum glycyrrhizanicum, stimulates mucose and increases syalic acids content.

2. Drugs protecting mucosa mechanically sucralfate (venter), Bismuth tricalii dicitus (De-Nol, Vis-Nol)

3. Complex drugs – Vicalinum, Vicairum

Sucralfate is a complex substance formed from a sulfated disaccharide and polyaluminum hydroxide. It polymerizes when the pH falls below 4. The condensed polymer forms a gel, which adheres to the base of a duodenal ulcer crater. When sucralfate is administered before meals, it is effective for the treatment of patients with duodenal ulcer disease. Adverse reactions are minimal because it is not systemically absorbed.

Choleretic drugs

Choleretic drugs stimulate bile secretion. They are divided into:

1. Drugs consist bile acids – cholenzymum, allocholum, and liobilum;
2. Synthetic drugs – oxaphenamidum;
3. Plant drugs – Cholosasum, Febicholum, flores Helichrysi arenarii, Styi cum Stigmatis Zea Maydis.

Cholecinetic drugs stimulate tonus of bile bladder – magnesii sulfas, and sorbitolum. **Cholespasmolytic drugs** have spasmolytic effect on biliary tract – atropini sulfas, platyphyllini hydrotartras, papaverini hydrochloridum, no-spanum, and magnesii sulfas. **Cholelytolytic drugs** solve cholesteryne concrements in bile bladder – chenofalk, ursofalk, olimentinum, and urolesanum. **Hepatoprotectors** increase stability of hepatocytes – esenciale, silimarinum, hepatobene, thiotriazolinum, antralam, acidum lipoicum etc. **Acidum lipolicum** increases energy metabolism of hepatocytes. Essenciale, silimarinum, hepatobene, thiotriazolinum, antralam are antioxidants.

Drugs decreasing pancreatic secretion

Proteolysis inhibitors decrease pancreas enzymes activity in the case of acute pancreatitis, pancreas cancer. Proteolysis inhibitors (contrycalum, gordox, pantripinum, trasilolum) inactivate trypsin circulating in blood, remove toxemia, block quinines, protect pancreas destruction and inhibit fibrinolysis.

Adverse effects: allergic reactions.

	Drug	Drug forms
1.	Tinctura Absinthii	Flac. 25ml
2.	Xenicalum	Caps. 0,12
3.	Pancreatinum	Pulv. ; Tab. 0,5
4.	Panzinormum	Dragee
5.	Contrykalum	30000 UA
6.	Pentagastrinum	Amp. 0,025% - 2ml
7.	Succus Gastricus Naturalis	Flac. 100ml

8.	Pepsinum	Pulv.
9.	Acidum Hydrochloricum Dilutum	Flac. 50ml
10.	Ranitidinum	Tab. 0,15; Amp. 2,5% - 1ml
11.	Famotidinum	Tab. 0,02, 0,04
12.	Pirenzepinum	Tab. 0,025; Amp. 0,01
13.	Omeprazolum	Caps. 0,02
14.	Natrii Hydrocarbonas	Pulv. ; Tab. 0,3, 0,5
15.	“Almagelum”	Flac. 150ml
16.	“Maalox”	Tab. ; Flac. 15ml
17.	De-nolum	Caps. 0,12
18.	Apomorphinum hydrochloridum	Amp. 1% 1ml
19.	Aethaperazinum	Tab. 0,004, 0,006, 0,01
20.	Metoclopramidum	Tab. 0,01; Amp. 0,5% - 2ml
21.	Allocholum	Tab.
22.	Cholenzymum	Tab.
23.	Cholosasum	Flac. 300ml
24.	Cholagolum	Flac. 10ml
25.	Oxaphenamidum	Tab. 0,25
26.	Magnesii Sulfas	Pulv.
27.	Essentiale Forte	Caps. ; Amp. 5ml

28.	Siliborum	Tab. 0,04
29.	Darsilum	Tab.
30.	Oleum Ricini	Flac. 30, 50ml; Caps. 1,0
31.	Bisacodylum	Dragée 0,005; Supp. rect. 0,01
32.	Senadexinum	Tab.
33.	Loperamidi hydrochloridum	Tab. 0,002
34.	Hylacum	Flac. 30, 100ml
35.	Bactisubtilum	Caps.

Drugs affecting haemopoiesis

Erythropoiesis stimulators (agents used to treat anemia)

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume. Anemia can be caused by chronic blood loss, bone marrow abnormalities, increased haemolysis, infections, malignancy, endocrine deficiencies and a number of other disease states.

The classification includes drugs used in hypochromic (iron-deficiency) anaemias, drugs used in hyperchromic anaemias and drugs used in anaemias due to chronic renal failure.

I. Drugs used in hypochromic (iron-deficiency) anaemias.

1. Iron preparations are divided into monodrugs, complex drugs, and also drugs for oral and parenteral administration.

1.1. Drugs for oral administration.

Ferri sulfas is a monodrug for oral administration. There are also **ferri fumaras**, **ferri gluconas**, and **ferri chloridum**. Most of these drugs have Fe^{2+} because Fe^{3+} may irritate the mucosa. In the stomach, iron is transformed into its ionic form. In the intestines, Fe^{2+} binds with protein apoferritin forming a ferritin complex, which is then transported to the blood. The active transport of Fe^{2+} is realized by Fe^{2+} complexes with amino acids, vitamins, or food.

peptides. In the blood serum Fe^{2+} separates and binds with β_1 globulin (transferrin), then this complex is transported to the bone marrow or to the depo tissues – liver and spleen. In the bone marrow Fe^{2+} is used to form haemoglobin and in depo tissues Fe^{2+} is stored in complex with apoferritin as ferritin. Iron may be used to form haemoglobin in erythrocytes, other haemin (myoglobin), non haemin enzymes (cytochrome – C – oxydase) and others.

Therapeutic uses: Iron deficiency, hypochromic anaemias, in chronic haemorrhage, iron malabsorption, pregnancy, and dystrophies.

Adverse effects: dyspepsia, constipation, teeth darkness, and nausea.

There are complex drugs such as **tardiferonum**, **actiferinum**, **ferroplex** and others.

?? Amino acids, riboflavinum, peptides, acidum hydrochloricum dilutum, acidum ascorbinicum, biometals (cobalt, magnesium, manganese, aurum), unbroken mucosa help absorption and calcium, antacids, tetracyclinum, laevomycesinum, fitates prevent absorption. If it impossible to administer drugs orally there are drugs for parenteral use such as Fercovenum, Ferrum lek and others. They have such **adverse effects** as hypotension, allergic reactions, nausea, vomiting.

Cobalt preparations such as **Coamidum** promotes iron absorption for haemoglobin synthesis, that is why it stimulates erythropoiesis.

Magnesium supports erythrocytes elastically.

II. Drugs used in hyperchromic anaemias - Cyanocobalaminum (B_{12} drug) and acidum folicum.

Cyanocobalaminum is biotransformed to cobalaminum, cofactor of acidum folicum reductase. It takes part in purine, pyrimidine, nucleic acids and protein synthesis. When there is deficit of Cyanocobalaminum the disturbances of bone marrow function take place and erythrocytes transform to megaloblasts. It is absorbed in pernicious anaemia. Deficiency of vitamin B_{12} can result from poor absorption due to the failure of gastric parietal cells to produce intrinsic factor (Castle factor). Cyanocobalaminum takes place in myelin synthesis, in formation of thiocompounds such as methioninum, glutathionum in regeneration and immune processes. Cyanocobalamines normalizes erythropoiesis, decreases neurological disturbances, impairment of tongue mucous, improves immune status.

Therapeutic uses: hyperchromic malignant, pernicious megaloblastic (Addison-Birmer

anemia), iron-deficiency, hypoplastic anemias, radiation diseases, nerve system diseases, other operations of immune deficits, in dystrophy.

Adverse effects: excitement, tachycardia, allergy, acceleration of coagulation, heartaches.

Acidum folicum takes purine, pyrimidine, nucleic acids, amino acids synthesis, in normal erythropoiesis, in regeneration, in leucopoiesis, thrombocytopoiesis, immune system activity.

Therapeutic uses: macrocytic anaemias (lactation, pregnancy, alcoholism etc), sprue, postoperative anemia, newborn babies, radiation diseases, chronic gastric enteritis.

Adverse effects: formations of concretions, B₁₂ concentration disease

III. Drugs used in anaemias due to chronic renal failure

Erythropoietin (epoetin, epres, epogenum) is a glycoprotein stimulating proliferation, differentiation of erythropoietic cell in bone marrow. Erythropoietin normalizes haemopoiesis and blood film.

Indications: anaemias in chronic renal failure, rheumatoid, arthritis, malignancy, AIDS, premature babies.

Adverse effects: headaches, arthralgia, edema, hypertension, dizziness.

Erythropoiesis inhibitors

Natrii phosphas marked with radioactive P³² decreases erythrocytes and thrombocytes content and is used in polycythaemia (erythroaemia).

Leukopoiesis stimulators are divided into:

1. Nucleic acids derivatives – Natrii nucleinas;
2. Pyrimidine derivatives – Pentoxylum, Methyluracylum etc.;
3. Colony stimulating factors – Filgrastimum, Malignostimum, Lenograstimum.

Derivatives of nucleic acids and pyrimidines stimulate synthesis of nucleic acids, proteins, which are sufficient for leucopoiesis, stimulate leukopoiesis, wound recovering, possess antiinflammatory action. Methyluracylum has cardiogenic effect.

Colony stimulating factors stimulate proliferation and differentiation of haemopoietic cells predecessors taking place in granulocytes, monocytes, macrophages formations.

Therapeutic uses: leucopenia in chemotherapy, radiation, intoxication. Methyluracylum is used in slow recovering, burns, fractures, ulcers. Colony stimulating factors are used in leucopenia lymphopenia, and agranulocytosis.

Adverse effects: nucleic acids derivatives, pyrimidine cause dyspepsia, colony stimulating factors – allergy.

Leukopoiesis inhibitors - glucocorticoids and antitumor agents (alkylating drugs, antimetabolites, antibiotics, alkaloids etc).

ANTICOAGULANT, ANTIPLATELET AND TROMBOLYTIC (FIBRINOLYTIC) DRUGS

1. Anticoagulants drugs.

1.1. Drugs of direct action:

- a) unfractionated heparinum (heparinum natrium, heparinum calcium);
- b) low-molecular-weight heparines: nandroparinum (fraxiparinum), dalteparinum (fragminum), enoxiparinum (clexanum), certoparinum-natrium (troparinum), and similar synthetic drug - fondapurinucs (aricstra)

1.2. Drugs of indirect action:

- a) cumarine derivatives (neodicumarinum, warfarinum, syncumar);
- b) indandione derivatives (phenylinum).

2. Fibrinolytic drugs - streptokinasum, urokinasum, and tissue type plasminogen activator (t-PA): alteplasum (actilise), tenecteplasum (metalise).

3. Antiaggregants.

3.1. Inhibitors of thromboxane A₂ synthesis:

- a) cyclooxygenase inhibitors – acidum acetylcysteinum;
- b) cyclooxygenase and thromboxanesynthetase inhibitors – indobuphenum.

3.2. Stimulators of prostacycline receptors – epoprostenolum.

3.3. Drugs protecting ADP action on thrombocytes – ticlopidinum (ticlidum), clopidogrel (plavix).

3.4. Drugs inhibiting phosphodiesterase – Dipyridamolum (Curantilum, Persantilum), Pentoxifyllinum (Agapurin, Trental)

3.5. Drugs blocking thrombocytes membranes glycoproteins II b/III a:

- a) monoclonal antibodies – Absiximabum;
- b) synthetic blockators glycoproteins II b/III a – Eptifibatidum (Aggrastatum), Tirofibanum (Integrilinum).

Heparinum binds to antithrombin III and induces a conformational change that accelerates the interaction of antithrombin III with coagulative factors. Heparinum also catalyzes the inhibition of conversion prothromin in thrombin, fibrinogen in fibrin. It gives negative charge to vessel and brakes aggregation to adhesion. Heparinum improves coronar vessels circulation. It exerts an antilipemic effect by releasing lipoprotein lipase from endothelial cells. Heparinum decreases platelet and inflammatory cells adhesiveness to endothelial cells, reduces of platelet – derived growth factor, inhibits tumor cell metastasis, exerts an antiproliferative effect on several types of smooth muscle. Low molecular-weight heparins depress activated Stuart-Prauers factor more than protrombinum and act longer.

Therapeutic use: Heparinum is used for prophylactic and treatment of vein thrombosis, lung artery thromboemboli, unstable angina pectoris, and myocardial infarction.

Adverse effects are: Hemorrhage, subdural hematoma, acute hemorrhagic pancreatitis, hemarthrosis, wound ecchymosis, thrombocytopenia, hypersensitivity reactions (rash, urticaria, pruritis, fever, alopecia, hypoaldosteronism, osteoporosis, ostealgia. Protamini sulfas is heparinum antagonist.

Drugs of indirect action. These drugs are vitamin K antagonists. Oral anticoagulants block epoxide reductase and creation of active form of vitamin K. They have anticoagulant effect and are used for prophylactic of thrombosis.

Adverse effects: hemorrhage, diarrhea, small intestine necrosis, urticaria, alopecia, skin necrosis, purple toes, dermatitis.

Fibrinolytic drugs

Mechanism of action: Streptokinasum, urokinasum, and t-PA all facilitate the conversion of plasminogen to plasmin. Plasmin is fibrinolytic. Streptokinasum acts indirectly, because it must interact with plasminogen to transform it into plasmin. Because t-PA is more selective than the kinases, it has a high affinity for fibrin and induces the degradation of plasminogen to plasmin only in the presence of fibrin. Alteplasmum (actilise), tenecteplasmum (metalise) have direct mechanism of action.

Pharmacokinetics: The plasma half-life of t-PA is 5 minutes, compared to 16

minutes for urokinasum and 23 minutes for Streptokinasum.

Therapeutic uses: t-PA, Streptokinasum, urokinasum have comparable efficacy in the reduction of mortality and improvement of left ventricular function. Drugs appear most effective when given less than 3 hours after the onset of symptoms. Thrombolytic therapy begins as soon as possible after the onset of symptoms of myocardial infarction. Streptokinasum is given by intravenous or intracoronary infusion. Urokinasum is infused into the occluded coronary artery. Drugs of t-PA are given by intravenous administration only.

Adverse effects and contraindications. Serious bleeding can occur; most important gastrointestinal and intracranial hemorrhages are possible. Streptokinasum can cause anaphylaxis. With any thrombolytic agent, cardiac arrhythmias can occur upon reperfusion of the occluded vessels. Contraindications to the use of thrombolytic agents include internal bleeding, cerebral vascular accident, recent intracranial or intraspinal trauma, or surgery, known bleeding diathesis, or severe uncontrolled hypertension. Any condition in which bleeding would be a significant hazard is a relative contraindication and calls for a careful risk-benefit analysis before using thrombolytic therapy.

Antiaggregants. Platelet aggregation is the most defense mechanism against leakage of blood from circulation. The antiaggregants must remove thromboxane A₂ ADP action, increase level of cAMP in thrombocytes, decrease Ca²⁺ concentration, block thrombocytes membranes glycoproteins II b/III a. These drugs are used for prophylactics of myocardial infarction, instable angina, for prophylactics of insults thrombosis, in case of angioplastics etc.

Drugs increasing coagulation for hemorrhage stopping

1. Coagulants (hemostatics).

1.1. For local applications – Spongia Haemostatica with ambenum; tachocorb (collagenum, fibrinogenum, thrombinum, aprotininum, ribofeavinum).

1.2. For systemic application – vicasolum, calcii chloridum, calcii gluconas; drugs of coagulation blood factors – factor IX (Ajmafex, immuninum); factor VII (Novosevenum), factor VIII (Immunatum, Ergopraecipitatum siccum), protamini

sulfas.

2. Aggregants.

3. Fibrinolysis inhibitors.

3.1. Aprotininum (Contricalum, Trasilolum, Gordox).

3.2. Acidum aminocapronicum (Pamba, Ambenum), Acidum tropexamicum (Cyclocapronum).

Etamsylatum (Dicenonum) has aggregant and angioprotective properties, decreases hemorrhage time, capillars permeability, increases quantity and physiological activity of thrombocytes.

Therapeutic use – hemorrhage after surgical operations, hemorrhage diathesis, other hemorrhages in urology, gynecology etc.

Contricalum (Aprotininum) inhibits plasmin and other proteolytic enzymes (trypsinogenum, quininum).

Therapeutic uses: fibrinolytic hemorrhage.

Adverse effects: hypotension, tachycardia, nausea, vomiting, allergic reactions.

Acidum aminocapronicum is conjugated with plasminogenum, inhibits its transformation into plasminum.

Therapeutic uses: fibrinolytic hemorrhage.

Adverse effects: hypotension, bradycardia, arrhythmias, dizziness.

№	Drug	Drug forms
1.	Ferri Sulfas	Pulv.; Caps. 1,0
2.	Fercovenum	Amp. 5ml
3.	Ferrum Lek	Amp. 2ml; Amp. 5ml
4.	Coamidum	Pulv.; Amp. 1% - 1ml
5.	Cyanocobalaminum	Amp. 0,003%, 0,01%, 0,02%,

		0,05% - 1ml
6.	Acidum Folicum	Pulv.; Tab. 0,001
7.	Methyluracilum	Pulv.; Tab. 0,5; Supp. rect. 0,5; Ung. 10% - 20,0
8.	Pentoxylum	Pulv.; Tab. 0,2,
9.	Natrii Nucleinas	Pulv.; Amp. 2%, 5% - 5, 10ml
10.	Heparinum	Flac. 5ml (5000, 10000, 20000 ED – 1ml)
11.	Warfarinum	Tab. 0,003
12.	Fraxiparinum	Spritz 1ml
13.	Phenylinum	Pulv.; Tab. 0,03
14.	Syncumar	Tab. 0,004
15.	Streptoliasum	Amp. 250000 ED, 500000 ED
16.	Actilyse	Flac. 0,02, 0,05
17.	Acidum Aminocapronicum	Flac. 5% - 100ml
18.	Dipyridamolum	Tab. 0,025, 0,075; Amp. 0,5% - 2ml
19.	Vikasolum	Tab. 0,015; Amp. 1% - 1ml
20.	Thrombinum	Amp. 125 UA, 250 UA (10ml)
21.	Calcii chloridum	Amp. 10% - 5, 10ml; Sol. 5% ad usum internum

22.	Etamsylatum	Tab. 0,25; Amp. 12,5% - 2ml
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Anti-Infective Agents

Antimicrobial agents are native or chemical substances which can kill or suppress the growth of microorganisms. There are antiseptics and disinfectants and chemotherapeutic agents. Antiseptics applied externally upon the skin and mucous membranes. Disinfectants are used for killing microorganisms in the environment (medical instruments, equipment, dishes, walls and floors of rooms etc.) Chemiotherapeutic agents influence definite types of microorganisms. **Antibiotics** are soluble compounds which are derived from certain microorganisms and which inhibit the growth of other microorganisms.

Antiseptics and disinfectants

These drugs are divided into two groups: 1) inorganic substances; 2) organic substances. Inorganic substances include 1) halogenes; 2) oxidizers; 3) heavy metals; 4) acids and alkalies. Organic substances include 1) phenol derivatives; 2) alcohols and aldehydes; 3) dyes; 4) detergents.

Halogens

The halogens include chlorine preparations (chloraminum, chlorhexidini bigluconas etc.) and iodine preparations (solutio iodi spirituosa, solutio Lugoli, ioddicerinum etc.). The mechanism of chlorine preparations action is associated with hypochlorite acid which decays into chlorine and oxygen. Chlorine takes place of hydrogen in NH-groups of microorganisms proteins and oxygen oxydizes essential enzymes of microorganisms. Chlorhexidini bigluconas has properties of detergents. Chloraminum is used for disinfection of environment, cloths, skin, endoscopes and non-metallic instruments. Chlorhexidini bigluconas indicates to process surgery skin area, surgeon's hands, patient's wounds, individual prophylaxis of sexually-transmitted diseases and quick sterilisation of instruments. Pantocidum is used for water disinfection.

Iodine is highly reactive element which takes place of hydrogen in NH-groups

of microorganisms proteins. Solutio Iodi spirituosa is used for disinfection of impaired skin areas, to process surgery skin area, surgeon's hands and patient's wounds. Solutio Lugoli is used for irrigation in otitis, tonsillitis, and atrophic rhinitis. Iodidicerinum is used for wounds treatment, irrigation in otitis, tonsillitis, and atrophic rhinitis, vaginitis, paradontosis.

Oxidizers

The mechanism of action of oxidisers (solutio Hydrogenii peroxydi diluta, Kalii permanganas, benzoili peroxydum) is associated with the release of oxygen which oxydizers the microbial proteins. Solutio Hydrogenii peroxidi diluta liberates oxygen mostly in molecular form which mechanically clean a wound. It is used for disinfection of impaired skin and mucous areas, irrigation of pus wounds. Kalii permanganas in solutions is used for mouthwash, gastric lavage, irritation and syringing in gynecology and urology, wounds and burns disinfections. Benzoili peroxydum is for skin processing in acne treatment.

Metallic salts

There are such drugs of heavy metals compounds 1) mercury salts (Hydrargyri dichloridum, ung. Hydrargyri oxydum flavum); 2) silver compounds (argenti nitras, protargolum, collargolum), 3) copper compounds (Cupri sulfas); 4) Zinc compounds (Zinci sulfas, Zinci oxydum) etc. They act as bacteriostatic by inactivating SH-groups of enzymes. They also may make albuminates in superficial layer of protoplasm (adstringential effect) or in a deep layer (scorching effect). When they denature proteins they cause necrotising effect. Hydrargyri dichloridum is used for outside disinfection. Ung. Hydrargyri oxydum flavum is indicated in pyoderma, pediculosis, blepharitis, keratitis, seborrhea treatment. Silver preparations are used in conjunctivitis, blenorrea, for the disinfection of wounds, urethra, urenary bladder. Argenti nitras in high concentrations is used as cauterizing agent in erosions, ulcers, surplus granulations. Zinci sulfas and Cupri sulfas are used in infections diseases of eyes and for the washing of the urethra and urinary bladder. Zinci oxydum is used for the disinfection of wounds, skin processing in eczemas, dermatitis, decubitus (bedsore).

Acids and alkalis

Acids (acidum boricum, acidum salicylicum, acidum benzoicum) and alkalis (Natrii tetraboras, Solutio Ammonii caustici).

The mechanism of these drug action is the denaturation of microbial proteins. Acidum boricum is used for the washing eyes, oral cavity, for the treatment some skin diseases. Acidum salicylicum is used as keratoplastic and keratolytic drug in dermatology. Acidum benzoicum, natrii tetraboras are used as antifungal agents. Solutio Ammonii caustici is indicated for the disinfection of surgeon's hands.

Phenol derivatives (Phenolum purum, resorcinum, vagotilum, ichthyolum, Pix liquida Betulae) cause the denaturation of microbial proteins (they have high solubility in lipids and penetrate well through the cell membranes). In low concentrations they block dehydrogenases. Phenoli purum is used for outside disinfection. Resorcinum is indicated in skin diseases (eczema, seborrhea, itches, fungal diseases). Vagotilum is derivative of tricresolum and is indicated in cervical erosion, inflammatory vaginal, urethra, cervical diseases, ulcers and granulation cauterization. Ichthyolum is used in burns, erysipelalous inflammation, eczema, pix liquida Betulae – in psoriasis, fungal infections, scabies.

Dyes

The group of dyes include Viride nitens, Methylenum coeruleum, Aethacridini lactas. Cations of dyes take place of anions of microorganisms and inhibit bacterial enzyme systems. They are used in cuts, scratches, skin pustules. Methylenum coeruleum is indicated in treatment of wounds, for cavities irrigation, pharyngeal and nasal mucous processing, treatment of poisoning with cyanides, carbon monoxide and other met-hemoglobin forming poisons.

Nitrofurantoin derivatives

The nitrofurantoin derivatives include furacilinum and furazolidonum. They act by inhibiting enzymes necessary for carbohydrate metabolism in bacteria after the reduction of nitrogroups. Furacilinum is used for processing of wounds, skin, mucous membranes, washing of the infected cavities. Furazolidonum is used of the urinari tract infections, intestinal infections, bacillary dysentery, paratyphoid, enteritis,

giardiasis (lambliosis).

Detergents

The detergents include a) cationic (Quaternary ammonium compounds) – cerigelum, degmicidum, aethonium, roccal, decamethoxinum, myramistinum, chlorhexidini bigluconas; b) anionic (Soaps) – sapo viridis. The mechanism of their action is decrease of the surface tension of the microbial cell membranes, which leads to the impairment of the osmotic balance and the causes of death of microorganisms. Cerigelum, degmicidum, chlorhexidini bigluconas, and roccal are used for processing of surgeon's hands, surgical area processing. Aethonium is used in mucous processing in keratitis, cornea ulceration, stomatitis and gingivitis. Decamethoxinum, myramistinum are used in fungal skin impairment, proctitis, ulcerative colitis, conjunctive, urinary bladder, mouth, bronchi irrigations. Sapo viridis is indicated for defogging of skin before operation and preparation of disinfectants solutions.

Types of anti-infective agents

Bacterial infections are readily treated in most instances by a wide variety of agents. Some antibacterial drugs are **bacteriostatic**; that is, they inhibit the growth of susceptible bacteria. Other antibacterials are truly **bactericidal**; that is, they kill susceptible bacteria. **Fungal infections**, in contrast to bacterial infections, generally are quite resistant to chemotherapy, and the number of useful agents for these infections is somewhat restricted. Fungal infections often occur as superinfections; that is, secondary infections superimposed on the original infection as a result of changes in the host flora. The drugs are divided in fungistatis and functional medicaments. **Mycobacterial infections: Tuberculosis** is one of the few diseases which requires a combination of antimicrobial drugs, which which are named tuberculostatic and tuberculocidal drugs. **There are drugs treatment of Helminthiasis, Protozoal infections, Viral infections**

General principles of anti-infective therapy. 1. Selection of an appropriate anti-infective agent includes: Identification of the infecting organism should precede antimicrobial therapy when possible. **2. Route of administration. 3. Optimal dose and concentration. 4. Rational antimicrobial combination therapy.**

5. Therapeutic responses to drug therapy should be monitored clinically and microbiologically to detect the development of resistance or superinfections. 6. The duration of drug therapy required depends on the pathogen, the site of infection, and the immunocompetence of the patient. 7. Inhibition of bacterial growth which continues after antibiotic blood concentrations have fallen to low levels is called the **postantibiotic effect (PAE)**. 8. Changes in hepatic and renal function – and the use of dialysis – can influence the pharmacokinetics of antimicrobials and may necessitate dosage modifications. 9. Antimicrobial therapy during pregnancy and neonatal period requires special consideration. Tetracyclines cause tooth enamel dysplasia and inhibition of bone growth. Sulfonamides, by displacing bilirubin from serum albumin, may cause kernicterus in the neonate. Laevomycetinum may cause a gray baby syndrome.

Antibiotics

Antibiotics are chemotherapeutic drugs of biological nature inhibiting microorganism selectively.

Antibiotics are divided according chemical structure:

1. Beta-lactam antibiotics (penicillins, cephalosporins, monobactams, carbopenems);
2. Macrolides and azalides;
3. Aminoglycosides;
4. Tetracyclines;
5. Laevomycetines;
6. Polyenes;
7. Glycopeptide antibiotics;
8. Lincosamides;
9. Polymyxines;
10. Steroid structure antibiotics;
11. Antibiotics of different chemical groups.

Classification according to mechanism of action:

1. Antibiotics disturb synthesis of bacterial cell wall – beta-lactam antibiotics, glycopeptides etc.;

2. Antibiotics disturb the initiation of protein synthesis – aminoglycosides antibiotics, tetracyclines, laevomycetines, macrolides, azalides, lincosamides, steroid structure antibiotics etc.;

3. Antibiotics impair permeability of cell wall – polymyxinum, polyene antibiotics etc.;

4. Antibiotics disturb nucleic acid synthesis – rifampicins etc.

Classifications according to types of action:

1. Bactericidal action – beta-lactam antibiotics etc.;

2. Bacteriostatic action – tetracyclines, laevomycetus etc.

Classification according to the spectrum of action:

1. Antibiotics influence on gram plus bacterias predominantly – native penicillins;

2. Antibiotics influence on gram negative bacterias predominantly – polymixins;

3. Antibiotics of wide spectrum of action – tetracyclinum – laevomycetinum, half synthetic penicillines, cefalosporines, carbopenemes, macrolides of the second generation rifampicinum etc.;

4. Antifungal antibiotics – amphotericinum, nystatinum etc.;

5. Anticancer antibiotics – doxorubinum etc.

Classification in nature:

1. Microbial nature of mold fungi – penicillinum etc.;

2. Microbial nature of Streptomyces – aminoglycosides etc.;

3. Bacterial nature – gramicidinum etc.;

4. Plant nature – novoimaninum etc.

Beta-lactam antibiotics

Penicillins, monobactamum, carbapenemum and cephalosporins are the major antibiotics which inhibit bacterial cell wall synthesis. They are called beta-lactams because of the unusual four-member ring which is common to all their members. These four large classes of beta-lactams include some of the most effective, widely used, and well-tolerated agents available for the treatment of microbial infections. The emergence of **microbial resistance** poses a constant challenge to the use of antimicrobial drugs. Mechanisms underlying microbial resistance to cell wall

synthesis inhibitors include the production of antibiotic-inactivating enzymes, changes in the structure of target receptors, and decreases in the permeability of microbes cellular membranes to antibiotics.

Mechanism of action: The beta-lactam antibiotics are **bactericidal**. The beta-lactam antibiotics inhibit key enzymes in bacterial cell wall synthesis. They are structurally resemble to the terminal d-alanyl-d-alanine (peptidoglycan-murein). Bacterial transpeptidase covalently bind beta lactam antibiotics on the enzyme active sites, the acyl-enzyme molecule is stable and inactive. They also appear to activate one or more cell-wall autolytic enzymes, causing lysis of the bacterium. **Beta-lactamases**, enzymes produced by many different bacteria, hydrolyze the beta-lactam ring, inactivating the antibiotic. **Penicillinase** and cephalosporinase are beta-lactamases with narrow substrate specificities. Initially sensitive bacterial strains can become permanently resistant to a particular antibiotic by acquiring plasmids or R (resistance) factors carrying the genetic code for a beta-lactamase.

Penicillins

Classification of Penicillins

I. Native penicillins

1.1. Drugs of short acting – Benzylpenicillinum natrium, Benzylpenicillinum calcium;

1.2. Drugs of long-acting – Penicillinum-novocainum, Bicillinum-1, Bicillinum-3, Bicillinum-5;

1.3. Drugs for oral administration - Penicillin G, Penicillin V (phenoxymethylpenicillinum);

II. Semisynthetic penicillins.

2.1. Penicillinase-resistant penicillins – Methicillinum, Oxacillinum, Cloxacillinum, Nafcillinum, Dicloxacillinum;

2.2. "Broad-spectrum" penicillins – Ampicillinum, Amoxicillinum, Bacampicillinum, Cyclacillinum, Hetacillinum, Pivampicillinum;

2.3. Antipseudomonas penicillins — Carbenicillinum - Carbenicillin indanyl, Ticarcillinum; Ureidopenicillinums - Aziocillinum, Mezlocillinum, Piperacillinum;

2.4. Combinations of penicillin and a beta-lactamase inhibitor Amoxicillin with clavulanic acid - Ampicillinum with sulbactam, amoxycyclinum with clavulanic acid, Ticarcillin with clavulanic acid.

Pharmacokinetics: Penicillins vary in their resistance to gastric acid and therefore vary in their oral bioavailability. They are polar compounds and are not metabolized extensively. They are usually excreted unchanged in the urine via glomerular filtration and tubular secretion, the latter process being inhibited by probenecid. Ampicillin and nafcillin are excreted partly in the bile. The plasma half-lives of most penicillins vary from one-half to 1 hour. Benzylpenicillinum is distributed widely throughout the body with about 60% reversibly bound to plasma albumin. It penetrates poorly into ocular, pericardial, and cerebrospinal fluids. Significant amounts of the drug appears in the liver, intestine, and kidney, as well as in bile, semen, and lymph. From 60%-90% of an intramuscular dose of benzylpenicillinum is excreted within 1 hour. Up to 99% of the dose is eliminated via the kidney; that is, about 90% by tubular secretion and 10% by glomerular filtration. Novocainum and benzathine forms of penicillin G are administered intramuscularly and have long plasma half-lives because the active drug is released very slowly into the bloodstream. Most penicillins cross the blood-brain barrier only when the meninges are inflamed. Because gastric acid inactivates **pheroxymethylpenicillinum**, only 30% of an oral dose is absorbed from the duodenum.

Mechanism of action: Penicillins inhibit the synthesis of bacterial cell walls and are considered **bactericidal**. They combine with and inactivate transpeptidase, which normally is responsible for cross-linking the linear glycopeptide strands of bacterial cell walls. Loss of cell wall rigidity in the presence of normal high intracellular osmotic pressure causes lysis of the bacterial membrane.

Pharmacologic effects and Therapeutic uses: The various types of penicillins differ in their spectrum of activity and in their degree of efficacy against particular species or strains. In general, microbial sensitivity should be verified whenever possible. **Benzylpenicillinum natrium and kalium** are highly effective

against many strains of gram-positive **cocci (streptococcal and staphylococcal) infections, *S. pneumoniae* (pneumococcal infections)**. They are the drug of first choice for treatment of pneumococcal pneumonia. For pneumococcal meningitis, benzylpenicillinum natrium is usually administered intravenously. Intrathecal administration is sometimes used, but arachnoiditis and encephalopathy can complicate this form of therapy. Other pneumococcal infections for which benzylpenicillinum natrium is the drug of first choice include suppurative arthritis, mastoiditis, endocarditis, pericarditis, and osteomyelitis, streptococcal pharyngitis and scarlet fever, otitis media. Benzylpenicillinum natrium and scarlet fever is the most effective treatment for all stages of syphilis, against many oral anaerobes, in gas gangrene, most strains of *Corynebacterium diphtheriae*, anthrax, actinomycosis, *Listeria* infections.

Benzylpenicillinum-novocainum action lasts 12 hours, Benzatin benzylpenicillinum (Bicillinum 1) - 7-10 days, Bicillinum - 3-7-10 days, Bicillinum-5 till a month. **Semisynthetic penicillins** are derivatives of 6-aminopenicillin acid. They are divided into:

- I. Drugs of narrow specter stabled to penicillinase (Oxacillinum, Doxacillinum).
- II. Drugs of wide specter.
 - 2.1 Ampicillinum, Amoxicillinum, Aminopenicillinum.
 - 2.2 Carloxyenicillinum, Carbenicillinum, Carfecillinum, Ticarcillinum.
 - 2.3 Ureidopenicillinum, Azlocillinum, Piperacillinum, Mezlocillinum.

Pharmacokinetics: Oxacillinum-natrium is stable in acidic stomach environment. Doxacillinum has more absorption. They influence gram-positive organism stable to native penicillinum. It is called antistaphylococcus penicillinum. Amoxicillinum is absorbed better than ampicillinum and acts longer.

Pharmacodynamics: Penicillinase-resistant penicillins has very narrow spectrum. This subclass of penicillins includes **methicillinum** (the prototype), **nafcillinum, and oxacillinum**. Their primary use is in the treatment of known or suspected staphylococcal infections. Methicillin-resistant staphylococci (MRSA) are

resistant to other members of this subgroup and may be resistant to multiple antimicrobial drugs. **Methicillinum** has one-twentieth the potency of Benzylpenicillinum-natrium. It is not administered orally because of poor absorption via this route. **Oxacillinum** is acid-stable and, therefore, can be given orally as well as intravenously and intramuscularly. It is highly protein-bound in the plasma. It is up to eight times as potent as methicillinum. **Cloxacillinum** has pharmacologic and pharmacokinetic properties which are similar to those of oxacillinum. **Nafcillinum** can be given orally, intravenously, or intramuscularly. **Dicloxacillinum**, because it is highly resistant to penicillinase and acid hydrolysis, is very effective when administered orally.

The broad-spectrum penicillins-ampicillinum, amoxicillinum, and their various derivatives (e.g. bacampicillin, pivampicillin, hetacillin) – are effective against gram-positive organisms, some strains of *E. coli*, *H. influenzae*, *Salmonella*, and *Shigella*, and some *Proteus* species. When strains are sensitive, ampicillin and amoxicillin are used to treat some forms of gonorrhoea, sinusitis and otitis media due to *H. influenzae*, pneumococci, or *S. pyogenes*, urinary tract infections due to *E. coli* or *P. mirabilis*, meningitis due to *H. influenzae*, meningococci, or pneumococci. Amoxicillinum influences more *Helicobacter pylori* and *S. pneumoniae*. **Broad-spectrum penicillins. Ampicillin and amoxicillin.** These drugs comprise a penicillin subgroup which has a wider spectrum of antibacterial activity than benzylpenicillinum but remains susceptible to penicillinases. Their clinical uses include indications similar to benzylpenicillin as well as infections due to enterococci, *Listeria monocytogenes*, *Escherichia coli*, *Proteus mirabilis*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, though resistant strains occur. When used in combination with inhibitors of penicillinases (clavulanic acid etc.), their antibacterial activity is enhanced. In enterococcal and listerial infections ampicillin is synergistic with aminoglycosides.

"Antipseudomonas" penicillins are chiefly used to treat serious infections (bacteremia, pneumonia, burn infections) due to gram-negative organisms, particularly *P. aeruginosa*, indole-positive *Proteus*, and *Enterobacter*.

Carbenicillinum and **ticarcillinum** have a spectrum or activity similar to that of ampicillin and, in addition, are effective against indole-positive *Proteus* and *Pseudomonas*. Ticarcillinum is two to four times more active against *P. aeruginosa* than carbenicillin is and may be preferable in serious *Pseudomonas* infections. The carbenicillin congener, **carbenicillin indanyl**, accumulates rapidly in the urine and, thus, provides effective therapy for urinary tract infections caused by indole-positive *Proteus* or *Pseudomonas*. **Azlocillinum**, **mezlocillinum**, and **piperacillinum** are known collectively as the **ureidopenicillins**. Aziocillinum and piperacillin are ten times more active than carbenicillin against *Pseudomonas* organisms. Mezlocillinum and piperacillinum are more active than carbenicillin against *Klebsiella*. When a *Pseudomonas* infection is life-threatening, antipseudomonas penicillin is often used in combination with gentamicin, amikacin, or tobramycin.

Combinations of penicillin and a beta-lactamase inhibitor

Clavulanic acid is a beta-lactamase inhibitor which is structurally related to the penicillins. Clavulanic acid extends the antibacterial spectrum of beta-lactam antibiotics by irreversibly binding and, thus, inhibiting many bacterial beta-lactamases. It extends in vitro activity of **amoxicillinum** to include beta-lactamase-producing strains of *H. influenzae*; *E. coli*, *Proteus* species; *Klebsiella pneumoniae*; *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*, as well as *S. aureus*; and *Branhamella catarrhalis*. It extends the in vitro activity of **ticarcillin** to include an extremely wide variety of gram-negative and gram-positive organisms and anaerobes. The combination of **amoxicillinum and clavulanate** (Amoxiclavum) is used to treat infections caused by beta-lactamase-producing strains of *H. influenzae*, *B. catarrhalis*, *S. aureus*, *E. coli*, *Klebsiella*, and *Enterobacter*. The combination of ticarcillin and clavulanate is used to treat infections caused by beta-lactamase-producing strains of *Klebsiella*, *E. coli*, *S. aureus*, *Pseudomonas*, *H. influenzae*, *Citrobacter*, *Enterobacter cloacae*, and *Serratia marcescens*.

Sulbactam is a penicillanic acid sulfone with limited antibacterial activity. Its principal action is to inactivate bacterial beta-lactamases, thereby enhancing the antibacterial spectrum of ampicillin. It extends the in vitro activity of **ampicillinum** to

include beta-lactamase-producing strains of *H. influenzae*, *E. coli*, *Proteus* species, *K. pneumoniae*, *S. aureus*, *S. epidermidis*, *B. catarrhalis*, *Enterobacter aerogenes*, *Acinetobacter calcoaceticus*, *Neisseria*, and several anaerobes, including *B. fragilis*. The combination of **ampicillinum and sulbactam** has been useful in treating intra-abdominal and gynecologic infections.

Bicillinum-1, 3, 5 have been shown to be effective prophylactically in the following conditions: rheumatic fever recurrences; syphilis; streptococcal infections (generalization).

Antipseudomonas penicillins. **Aziocillinum** is given intravenously. **Carbenicillinum, ticarcillinum, mezlocillinum,** and **piperacillinum** are given intravenously or intramuscularly. **Piperacillinum and ticarcillinum:** These drugs have activity against several gram-negative rods, including pseudomonas, enterobacter, and in some cases klebsiella species. More drugs in this subgroup have synergistic actions when used with aminoglycoside against such organisms. Piperacillinum and ticarcillinum are susceptible to penicillinases and are often used in combination with penicillinase inhibitors to enhance their activity. **Carbenicillinum indanyl** is acid-stable and is administered orally.

Combinations of penicillinum and a beta-lactamase inhibitor. **Amoxicillinum with clavulanate** is given orally. **Ticarcillinum with clavulanatum** is given intravenously. **Ampicillinum with sulbactam** is given intravenously or intramuscularly.

Adverse effects. Hypersensitivity reactions to the penicillinums occur in 5%-20% of patients receiving these drugs, and all forms of penicillin can cause hypersensitivity reactions. A reaction can occur in the absence of prior therapeutic penicillin administration. The reaction can range from a mild rash to life-threatening anaphylaxis and may persist 1-2 weeks after discontinuation of therapy. Hypersensitivity reactions include: skin rashes of all types. In severe cases, the Stevens-Johnson syndrome can occur. The highest incidence of skin rash (about 9%) occurs after ampicillin administration. Fever, which disappears within 36 hours after termination of administration, eosinophilia, angioedema, serum sickness,

anaphylactic reactions. One in 50,000 patients treated with penicillin dies from this type of reaction, which is the most common after parenteral administration, but it can occur after oral ingestion and with minute quantities of penicillin; recurrent reactions and cross-sensitivity. A hypersensitivity reaction to one form of penicillin places the affected patient at high risk of reaction. The risk of cross-reactions with other beta-lactams is less clear. Penicillin-allergic individuals occasionally have allergic reactions to cephalosporins. In penicillin-allergic patients serious infections due to gram-positive organisms are often treated with vancomycin. Alternatives for other infections include erythromycin, trimethoprim-sulfamethoxazole, aminoglycosides, and ciprofloxacin.

Gastrointestinal complications are more likely with orally administered preparations; an example is ampicillin-associated diarrhea. Amoxicillinum is thought to cause a lower incidence of diarrhea than ampicillin.

Nephrotoxicity is very rare. Bone-marrow toxicity is uncommon. Agranulocytosis has been reported with ampicillin administration. Impairment of platelet aggregation has been reported with carbenicillin administration. Superinfection results from alterations in intestinal flora. A low incidence occurs with penicillin G administration. A higher incidence occurs with broad-spectrum penicillins, such as ampicillin and carbenicillin.

Cephalosporins

The cephalosporins are derivatives of 7-aminocephalosporanic acid and contain the beta-lactam ring structure and are semisynthetic.

Classification. The cephalosporins are typically classified by "generations", which roughly parallel to their chronologic development and their antimicrobial spectrum.

First-generation drugs: Cefazolinum (parenteral) and **cephalexinum** (oral), **cefadroxilum**, **cefalotinum**, **cefapirinum** are examples of this subgroup. They are active against gram-positive cocci, including staphylococci and common streptococci. Many strains of *E coli* and *K pneumoniae* are also sensitive. Clinical uses include treatment of infections caused by these organisms and surgical prophylaxis in

selected conditions. These drugs have minimal activity against gram-negative cocci, enterococci methicillin-resistant staphylococci, and most gram-negative rods.

Second-generation drugs: Drugs in this subgroup usually have less activity against gram-positive organisms than the first-generation drugs but have an extended gram-negative coverage. Marked differences in activity occur among the drugs in this subgroup. Examples of clinical uses include infections caused by *Bacteroides fragilis* (**cefotetanum, cefoxitinum**) and by *H influenzae* or *Moraxella catarrhalis* (**cefuroximum, cefaclor etc.**).

Third-generation drugs: Characteristic features of third-generation drugs (e.g. **cefoperazonum, cefodizimum, cefpiramidum, cefpodoximum, ceftributenum, moxalactamum, cefotaximum etc.**) include increased activity against gram-negative organisms resistant to other beta-lactam drugs and ability to penetrate a blood-brain barrier (except cefoperazone and cefixime). Most are active against enterobacter, providencia, *Serratia marcescens*, and beta-lactamase-producing strains of *H influenzae* and neisseria. Individual drugs also have activity against *B.pseudomonas* (ceftazidinum) and *B.fragilis* (**ceftizoximum**). Drugs in this subclass should usually be reserved for treatment of serious infections, e.g. bacterial meningitis. **Ceftriaxonum** (parenteral) and **cefiximum** (oral), currently drugs of choice in gonorrhoea, are exceptions. Likewise, in acute otitis media, a single injection of ceftriaxone is as effective as a 10-day course of treatment with amoxicillin or cefaclor.

Fourth-generation drugs: **Cefipimum, cefpiromum, cefclidinum, cefluprenamum, cefosopranum, cefquinomum** are more resistant to beta-lactamases produced by gram-negative organisms, including enterobacter, haemophilus, and neisseria. Cefipimum combines a gram-positive activity of first-generation agents with a wider gram-negative spectrum of third-generation cephalosporins.

Mechanism of action: Cephalosporins, like the penicillins, inhibit bacterial cell wall synthesis and are considered **bactericidal**. Cephalosporins are bactericidal against susceptible organisms. Structural differences from penicillins render cephalosporins less susceptible to penicillinases produced by staphylococci, but

many bacteria are resistant through the production of other beta-lactamases which can inactivate cephalosporins. Resistance can also result from damages in membrane permeability to cephalosporins and from changes in PBPs. Some bacteria elaborate a beta-lactamase called **cephalosporinase** which acts on the cephalosporin nucleus to destroy its antibacterial activity, but many cephalosporins are resistant to the enzyme.

Pharmacokinetics: Most cephalosporins are administered parenterally; some, however, are well absorbed from the gastrointestinal tract and can be given orally. Several cephalosporins are available for oral use, but most are administered parenterally. Cephalosporins with side-chains may undergo hepatic metabolism, but the major elimination mechanism for drugs in this class is renal excretion via active tubular secretion. Cefoperazonum and ceftriaxonum are excreted mainly in the bile. Most first- and second generation cephalosporins do not enter the cerebrospinal fluid even when the meninges are inflamed. The cephalosporins become widely distributed throughout body tissues and fluids. The majority does not penetrate a blood-brain barrier and, thus, are not effective in the treatment of the CNS infections. Some cephalosporins are excreted via the bile, most are excreted in the urine via renal tubular secretion. Probenecid blocks the tubular secretion of cephalosporins, often resulting in an increased half-life and elevated plasma concentration.

Pharmacologic effects: According the generations all cephalosporins are active against different microorganisms.

Therapeutic uses: Diseases produced by *S. aureus*, both penicillin-sensitive and penicillin-resistant, including skin infections, osteomyelitis, and endocarditis, respond favorably to the cephalosporins. Cephalosporins are the drugs of first choice for *K. pneumoniae* infections. These drugs are used successfully in the treatment of pneumococcal pneumonia and in infections caused by *S. pyogenes*. Some of the parenteral cephalosporins are efficacious in the treatment of gonococcal disease which is resistant to other agents. Diseases caused by a number of gram-negative bacteria, including respiratory and urinary tract infections, respond well. The expanded-spectrum of activity of the cephalosporins includes effectiveness against *Proteus*, *B. fragilis*, *Serratia*, *Enterobacter*, and some activity against *Pseudomonas*.

These agents are effective for the treatment of meningitis caused by susceptible strains.

First-generation cephalosporins are *not* effective against indole-positive *Proteus*, *Pseu-domonas*, *Serratia*, *Enterobacter*, or *B. fragilis*. **Cephalothinum**. It is not well absorbed from the gastrointestinal tract. It is usually given intravenously. Intramuscular injection is painful. It is excreted principally via renal tubular secretion. **Cefazolinum**. It is not well absorbed from the gastrointestinal tract and is administered intravenously or intramuscularly. Some 80% of the drug is reversibly bound to plasma proteins, substantially increasing its half-life. Cefazolinum is eliminated primarily by renal glomerular filtration; renal tubular secretion and biliary secretion play secondary roles. **Cephalexinum**. It is well absorbed from the gastrointestinal tract because of its high acid stability. It is available in oral capsules, suspensions, and pediatric drops. More than 90% of this drug is excreted unchanged in the urine; it is also excreted into bile. **Cephradinum** is similar to cephalixin. It can be given orally, intravenously, or intramuscularly. **Cefadroxilum** is an orally active analogue of cephalixin. It is used in the treatment of urinary tract infections.

Second-generation cephalosporins. **Cefamandolum**. This expanded-spectrum cephalosporin is effective against indole-positive *Proteus* and beta-lactamase-producing *H. influenzae*. It is administered parenterally only. **Cefoxitinum**. This expanded-spectrum cephalosporin is effective against indole-positive *Proteus* and *B. fragilis*. It has less activity against the gram-positive organisms. It is given parenterally. **Cefaclor** is similar to cephalixin but also is effective against beta-lactamase-producing *H. influemae*. It is given orally. **Cefonicidum** has an antibacterial spectrum similar to that of cefamandole. Its extended half-life allows once-a-day dosing; it is given parenterally. **Cefuroximum** is an expanded-spectrum cephalosporin which is useful for serious *H. influenzae* infections, particularly respiratory tract infections and otitis media. It is available for both parenteral and oral administration. **Ceforanidum** is similar in structure to cefamandole but is less active against *H. influenzae*. It is given parenterally. **Cefotetanum** has the in vitro spectrum similar to that of cefoxitin, but it is less active against some anaerobes. It is given

parenterally.

Third-generation cephalosporins. Cefotaximum, ceftizoximum, and ceftriaxonum. These relatively new, semisynthetic cephalosporins are more potent than the parent drug. They are given parenterally. Ceftriaxonum, because of its long half-life, can be administered once a day. It is particularly useful against penicillinase-producing strains of *Neisseria gonorrhoeae*. **Cefoperazonum and ceftazidimum** have greater activity against *P. aeruginosa* than the other third-generation cephalosporins but lesser activity against some other organisms. **Cefiximum** is effective against beta-lactamase-producing strains of *H. influenzae*. It can be administered orally once a day.

Fourth generation cephalosporins. Cefepimum is effective to gram-positive and gram-negative microorganism. Only some strains of *Xanthomonas multiphilis* are stable to the drug.

Adverse effects. Hypersensitivity reactions occur in about 5% of patients receiving cephalosporin therapy. Cephalosporins, like penicillins, elicit a spectrum of reactions which range from mild skin rash to anaphylaxis. A cross-sensitivity reaction to the cephalosporins occasionally occurs in individuals who are allergic to penicillin. Renal damage, although rare with normal doses of cephalosporins, can occur. Local tissue reactions can occur with parenteral administration. Intravenous administration can cause thrombophlebitis. Superinfections caused by gram-negative bacteria or yeasts can occur following administration of the cephalosporins. Moxalactam can induce a bleeding diathesis and cephaloridine is nephrotoxic.

Carbapenems

Thienamum (Imipenemum and Cilastatinum) and meropenemum. These drugs are **carbapenems** (chemically different from penicillins but retaining the beta-lactam ring structure) with low susceptibility to beta-lactamases. The drugs have ultrawide activity against gram-positive cocci (including some penicillin-resistant pneumococci), gram-negative rods, and anaerobes. They are administered parenterally and are especially useful for infections caused by organisms resistant to other antibiotics. They are currently the drug of choice for infections due to

enterobacter. Imipenem is inactivated by renal dehydropeptidase I and is administered in combination with cilastatinum, an inhibitor of this enzyme as Thienamum. Thienamum increases the plasma half-life of imipenemum and inhibits the formation of a potentially nephrotoxic metabolite.

Adverse effects of Thienamum include gastrointestinal distress, skin rash, and, at very high plasma levels, the CNS toxicity (confusion, encephalopathy, seizures). There is partial cross-allergenicity with the penicillins. **Meropenem** is similar to imipenem except that it is not metabolized by renal dehydropeptidases and is less likely to cause seizures.

Pharmacokinetics: Imipenemum is given in combination with cilastatin, a dipeptidase inhibitor which inhibits the renal tubular metabolism of imipenemum and prevents the formation of potentially nephrotoxic compounds. The serum elimination half-life of both imipenem and cilastatin is 1 hour. Imipenemum is filtered and secreted by the kidney, and if given alone, it is inactivated by a dipeptidase enzyme in the kidney, which opens the beta-lactam ring. Meropenemum has similar pharmacokinetics.

Pharmacologic effects: Thienamum and meropenemum have the broadest antimicrobial spectrum of all the beta-lactam antibiotics. They are active against both gram-positive and gram-negative cocci (except methicillin-resistant staphylococci), Enterobacteriaceae, *P. aeruginosa*, and anaerobic bacteria, including *B. fragilis*. Gonococci and *H. influenzae* strains which are resistant to both penicillin and ampicillin are susceptible to them.

Therapeutic uses: Use of Thienamum and Meropenemum is limited to the treatment of serious hospital-acquired infections due to susceptible organisms. They are given intravenously. They are used in urinary tract, respiratory tract, skin, and soft tissue infections. It is effective for the treatment of osteomyelitis, septic arthritis, bacteremia, and gynecologic and intra-abdominal infections. Their usefulness in staphylococcal endocarditis has been established, but not in the CNS infections.

Adverse effects: *P. aeruginosa* may become resistant during carbopenems therapy. Allergic reactions. Patients allergic to penicillin should be considered

allergic to them. Nausea, vomiting, and diarrhea occur.

Monobactams

Aztreonam is a **monobactam** which is resistant to beta-lactamases produced by certain gram-negative rods, including *Klebsiella*, *Pseudomonas*, and *Serratia*. The drug has no activity against gram-positive bacteria or anaerobes. It is an inhibitor of cell wall synthesis, preferentially binding to PBP3, and is synergistic with aminoglycosides. Aztreonam is administered intravenously and is eliminated via renal tubular secretion. Its half-life is prolonged in renal failure. Adverse effects include gastrointestinal upset with possible superinfection, vertigo and headache, and rare hepatotoxicity. Though skin rash may occur, there is no cross-allergenicity with penicillins.

Mechanism of action: Like other beta-lactams, aztreonam interferes with the synthesis of the bacterial cell wall.

Pharmacologic effects: Aztreonam is highly resistant to beta-lactamases. It is highly active against aerobic gram-negative bacteria, including *P. aeruginosa* and penicillinase-producing strains of *H. influenzae* and gonococci. It shows poor activity against gram-positive cocci and anaerobic bacteria.

Therapeutic uses: Aztreonam is substituted by aminoglycosides in the treatment of urinary tract, lower respiratory tract, and skin and soft tissue infections. Additionally, osteomyelitis, gonorrhea, and gynecologic and intra-abdominal infections due to susceptible pathogens have been successfully treated. Because of its narrow spectrum aztreonam is often used in combination with another antimicrobial agent. Aztreonam is administered parenterally.

Adverse effects: Colonization and superinfection with gram-positive cocci can occur. Pseudomembranous colitis has been reported. Aztreonam shows little or no immunologic cross-reactivity with other beta-lactams.

Beta-Lactamase Inhibitors: Clavulanic acid, sulbactam, and tazobactam are used in fixed combinations with certain hydrolyzable penicillins. They are most active against plasmid-encoded beta-lactamases such as those produced by gonococci, streptococci, *E. coli*, and *H. influenzae*. They are not good inhibitors of

inducible chromosomal beta-lactamases formed by enterobacter and pseudomonas. There are combined drugs: amoxiclavum (amoxycillinum + clavulanic acid); unasinum (ampicillinum + sulbactam) etc.

Aminoglycosides

The aminoglycosides are compounds containing characteristic amino sugars joined to a hexose nucleus in glycosidic linkage. They are polycations and their polarity accounts for their pharmacokinetic properties. **Modes of antibacterial action:** in the treatment of microbial infections with antibiotics, multiple daily dosage regimens traditionally have been designed to maintain serum concentrations above the minimal inhibitory concentration (MIC) for as long as possible. Aminoglycosides are also capable of exerting a postantibiotic effect such that their killing action continues when their plasma levels have declined below measurable levels. Consequently, aminoglycosides have greater efficacy when administered as a single large dose than when given as multiple smaller doses. The toxicity (in contrast to the antibacterial efficacy) of aminoglycosides depends both on a critical plasma concentration and on the time which such a level exceeds.

Mechanism of action: Aminoglycosides are bactericidal inhibitors of protein synthesis. Their penetration through the bacterial cell envelope is partly dependent on oxygen-dependent active transport and they have little activity against strict anaerobes. Aminoglycoside transport can be enhanced by cell wall synthesis inhibitors, which may be the basis of antimicrobial synergism. Inside the cell aminoglycosides bind to the 30S ribosomal subunit and interfere with protein synthesis in at least three ways: they block formation of the initiation complex; they cause misreading of the code on the mRNA template; and they inhibit translocation. Aminoglycosides may also disrupt polysomal structure, resulting in nonfunctional monosomes. The aminoglycosides inhibit protein biosynthesis by acting directly on the ribosome. They interfere with the proper attachment of messenger RNA to ribosomes in the initiation of protein synthesis. They also cause misreading of the genetic code and, hence, cause decreased or abnormal protein synthesis. The aminoglycosides also appear to disrupt the bacterial cytoplasmic

membrane. The rapid **bactericidal** effect of the aminoglycosides is not, however, adequately explained by any of their known actions. Aminoglycosides include 1) first generation – streptomycin, monomycin, neomycin, and kanamycin; 2) second generation – gentamicin; 3) third generation – tobramycin, sisomicin, netilmicin, and amikacin; 4) fourth generation – isepamicin, dactinomycin, and arbekacin.

Pharmacokinetics: Aminoglycosides are polar compounds polycationic structure and are not absorbed after oral administration. They must be given parenterally for systemic effect absorbed rapidly and have limited tissue penetration. They are distributed in all extracellular fluids, but tissue concentrations are low except in the kidney and ear. They cross a blood-brain barrier only if the meninges are inflamed.

Microbial resistance: The primary mechanism of resistance to aminoglycosides involves a plasmid-mediated formation of inactivating enzymes. Amikacin and netilmicin are not affected by most aminoglycoside-inactivating enzymes which cause bacterial resistance in some species.

Pharmacologic effects. Streptomycin. High concentrations of streptomycin are bactericidal; low concentrations are bacteriostatic. Streptomycin is effective against the organisms which cause plague (*Yersinia pestis*) and tularemia (*Francisella tularensis*) and, in combination with penicillin, against gram-positive enterococci and streptococci. In vivo, streptomycin suppresses tubercle bacilli. **Neomycin** is effective against many gram-negative species and is also effective against several gram-positive bacteria (e.g. *S. aureus*). Streptococci are generally resistant to neomycin. **Gentamicin** is bactericidal against a wide variety of gram-negative organisms, including indole-positive *Proteus*, *Pseudomonas*, and *Serratia* organisms. Some strains of *Staphylococcus* may be sensitive to gentamicin. **Tobramycin** has a spectrum of activity similar to that of gentamicin but may be slightly more effective against *Pseudomonas*. **Amikacin** has also a spectrum of activity similar to that of gentamicin but often is reserved for situations in which resistance to gentamicin emerged.

Netilmicinum has a spectrum of activity similar to that of amikacinum and may be active against bacteria which are resistant to gentamicinum. **Kanamycinum** has a more limited spectrum of activity than gentamicinum has. It is ineffective against *Pseudomonas* and most gram-positive organisms. Kanamycinum, amikacinum, streptomycinum, and neomycinum all have some activity against *M. tuberculosis*. Anaerobic microorganisms are generally resistant to the aminoglycosides.

Therapeutic uses: Streptomycinum is used very seldom. Subacute bacterial endocarditis caused by the viridans group of streptococci or by enterococci usually in combination with benzylpenicillinum-natrium or oxacillinum-natrium. Because of the frequent development of bacterial resistance, streptomycinum is used alone to treat only two infections – tularemia and plague. Severe cases of brucellosis are treated with a combination of streptomycinum and tetracyclinum. Urinary and respiratory tract infections, peritonitis, and bacterial meningitis may respond to streptomycinum but are treated more effectively with other agents. Although streptomycinum is no longer used alone in the treatment of pulmonary tuberculosis, it is often used in combination with other agents for the treatment of serious forms of tuberculosis.

Gentamicinum, tobramycinum, amikacinum, and netilmicinum. May be used in treatment of many infections can be treated successfully with these agents, but their toxicity restricts their use to situations involving life-threatening infections caused by: *P. aeruginosa*, *Serratia*, *Enterobacter*, and *Klebsiella*; methicillin-resistant staphylococci which are sensitive to gentamicinum. These agents are sometimes used as part of an initial "blind therapy" for serious infections of unknown etiology, in which case a penicillinumase-resistant penicillinum or a cephalosporin is administered in combination with an aminoglycoside, such as gentamicinum.

Neomycinum, because of its serious toxic effects when absorbed systemically, is used most frequently in dermatologic and ophthalmic ointments. In addition, neomycinum can be used orally as a bowel preparation for surgery or for the management of hepatic coma. **Kanamycinum** has also been largely superseded by less toxic, more effective agents.

Adverse effects: All of the aminoglycosides have a narrow therapeutic index

which limits their parenteral usage. Ototoxicity and nephrotoxicity are the most serious side effects. Both labyrinthine damage and vestibular disturbances can occur. Gentamicinum is the most nephrotoxic of the aminoglycosides. It can produce acute renal insufficiency and tubular necrosis. Neurotoxic effects include dysfunction of the optic nerve can occur with streptomycinum, producing scotomas, neuritis, psychosis. Neuromuscular junction blockade may result when an aminoglycoside is given at high doses and in combination with curariform drugs. This apparently results from a decreased sensitivity of the postjunctional membrane to acetylcholine and decreased presynaptic release of the transmitter. Hypersensitivity reactions can occur. Superinfection and intestinal malabsorption can occur following oral administration of neomycinum.

Tetracyclines

Tetracyclines are divided into 1) natural - Oxytetracyclinum, Tetracyclinum;
2) semisynthetic - Doxycyclinum, Methacyclinum, Minocyclinum.

Tetracyclinum and its congeners are derivatives of the polycyclic naphthacenecarboxamide. Tetracyclinum are broad-spectrum antibiotics with activity against gram-positive and gram-negative bacteria, rickettsia, chlamydia, mycoplasma, and some protozoa. Susceptible organisms accumulate tetracyclinum intracellularly via energy-dependent transport systems in their cell membranes. Plasmid-mediated resistance to tetracyclinum is widespread. Resistance mechanisms include decreased activity of the uptake systems and the development of mechanisms (efflux pumps) for active extrusion of tetracyclinum.

Mechanism of action: Tetracyclinum are primarily **bacteriostatic**, inhibiting protein synthesis by binding to 30S ribosomes. Tetracyclinum affects both eukaryotic and prokaryotic cells but apparently penetrates microbial membranes more readily due to the presence of active transport systems in microbes.

Pharmacokinetics: Tetracyclinum are adequately but incompletely absorbed from the gastrointestinal tract, particularly from the stomach and upper small intestine. Oral absorption is variable, especially for the older drugs, and may be impaired by food and multivalent cations (calcium, iron, aluminum).

Tetracyclines have a wide tissue distribution and cross the placental barrier. All of the tetracyclines undergo enterohepatic cycling. Doxycycline is excreted mainly in feces; the other drugs are eliminated primarily in the urine. The half-lives of doxycycline and minocycline are longer than those of other tetracyclines. Absorption is impaired by food, especially milk and milk products, by aluminum hydroxide gels and by calcium and magnesium salts. **Minocycline** and **doxycycline** are exceptions in that they chelate poorly with calcium, and food does not interfere with their absorption. Like other tetracyclines, they do chelate with iron to form insoluble complexes. The tetracycline diffuses into body fluids and binds to plasma proteins to varying degrees, depending on the particular preparation. Concentrations in the cerebrospinal fluid are about 20% of serum levels unless the meninges are inflamed. The tetracyclines are removed from the blood by the liver and are excreted into the intestine by way of the bile. They undergo enterohepatic circulation. Excretion occurs primarily via the kidney, although there is some fecal excretion. Renal clearance of these drugs is by glomerular filtration. Gram-positive bacteria often become resistant to the tetracyclines, limiting the usefulness of these drugs.

Pharmacologic effects: Tetracyclines are effective against many gram-positive and gram-negative bacteria. The tetracyclines are effective against *Mycoplasma*, *Borrelia*, *Chlamydia*, and rickettsial species. They are useful secondary drugs against *Leptospira* and *Treponema* species. In high concentrations the tetracyclines inhibit the growth of the protozoan *Entamoeba histolytica*.

Therapeutic uses: The use of tetracyclines for treatment of infectious disease has declined because of increasing bacterial resistance and the development of newer, more effective antimicrobial agents. Tetracyclines are useful in the treatment of the following conditions. **Rickettsial infections.** Tetracyclines are the drugs of first choice for these diseases, which include: Rocky Mountain spotted fever, Brill's disease, murine and scrub typhus, rickettsialpox, Q fever. **Chlamydial infections:** lymphogranuloma venereum, psittacosis, inclusion conjunctivitis, trachoma. **Mycoplasmal infections.** **Bacillary infections:** brucellosis, tularemia, cholera, some *Shigella* and *Salmonella* infections. **Venereal infections:** gonorrhea,

syphilis, chancroid, granuloma inguinale, chlamydial urethritis or cervicitis. **Amebiasis. Lyme disease**, a multisystem inflammatory disorder, is caused by the spirochete *Borrelia burgdorferi*, which is transmitted by ticks. Oral tetracycline or doxycycline for 10-20 days shortens the duration of symptoms and often prevents the development of more serious sequelae. Staphylococcal and streptococcal infections may respond to tetracycline. The drugs are third-line agents against these infections. In urinary tract infections, the use of tetracycline is limited because of the increasing number of resistant microorganisms. Tetracycline may be beneficial in the treatment of acne.

The various tetracyclines include: **Oxytetracycline, Tetracycline, Doxycycline, Methacycline. Minocycline** - absorption of this drug is not impaired by food or calcium ion. **Doxycycline**: increased absorption of doxycycline allows once-daily administration after the first day; as with minocycline, food and calcium ions do not affect absorption; as opposed to the other tetracycline, 90% of this drug is excreted in the feces; therefore, it does not accumulate in the blood of patients with compromised renal function. Thus, it is one of the safest tetracycline for use against extrarenal infections in patients with renal dysfunction.

Adverse effects: Hypersensitivity reactions, including skin rash and drug fever, can occur. Cross-sensitivity among the various tetracycline is common. When tetracycline are administered orally, gastrointestinal irritation is common. The intravenous administration of tetracycline often produces thrombophlebitis due to local irritation. Intramuscular injections are painful, cause local irritation, and result in poor absorption of the drugs. High doses of tetracycline can produce hepatic dysfunction. This reaction is exacerbated during pregnancy. Children receiving tetracycline may develop yellow-brown discoloration of the teeth and suffer depressed bone growth. The drugs are deposited in the teeth and bones because of their chelating properties and form a tetracycline-calcium orthophosphate complex. Discoloration of the permanent teeth can result, however, from the administration of tetracycline at any time between the ages of 2 months and 7

years, the period of tooth calcification. Tetracyclinum treatment during pregnancy can produce discoloration of the teeth in the offspring. The ingestion of outdated and degraded tetracyclinum can result in a form of the Fanconi syndrome (renal tubular dysfunction, which can lead to renal failure). Tetracyclinum can cause increased intracranial pressure, especially in infants. Vestibular toxicity can occur with following minocyclinum therapy. Superinfection by strains of resistant bacteria and yeasts is a significant problem which can result in staphylococcal enterocolitis, intestinal candidiasis, and pseudomembranous colitis.

Laevomycetinum is a nitrobenzene derivative, the antimicrobial drugs selectively inhibit bacterial protein synthesis, influence 50S ribosomes.

Mechanism of action: Laevomycetinum inhibits protein synthesis by acting on the 50S ribosomal subunit, a site of action shared with macrolide antibiotics and clindamycin. Laevomycetinum indirectly inhibits transpeptidation (catalyzed by peptidyl transferase) by blocking the binding of the aminoacyl moiety of the charged tRNA molecule to the acceptor site on the ribosome-mRNA complex. Thus, the peptide at the donor site cannot be transferred to its amino acid acceptor. This drug is primarily **bacteriostatic**, although it may be bactericidal to some strains.

Pharmacokinetics: Laevomycetinum is absorbed rapidly from the gastrointestinal tract. The drug undergoes enterohepatic cycling and a small fraction of the dose is excreted in the urine unchanged. Most of the drug is inactivated by a hepatic glucuronosyltransferase. It is widely distributed in body fluids and reaches therapeutic levels in cerebrospinal fluid. It is also present in bile, milk, and aqueous humor. Laevomycetinum is metabolized in the liver by glucuronyl transferase. Its metabolites are excreted in the urine.

Pharmacologic effects: Laevomycetinum has a fairly wide spectrum of antimicrobial activity, including: many gram-negative organisms (e.g. it is bactericidal for *H. influenzae*); anaerobic organisms, such as *Bacteroides* species (e.g. *B. fragilis*); some strains of *Streptococcus* and *Staphylococcus* (at a high antibiotic concentration); species of *Clostridium*, *Chlamydia*, and *Mycoplasma*; rickettsiae in which it suppresses growth. *P. aeruginosa* is resistant.

Therapeutic uses: Potentially severe toxicity limits the use of Laevomycetinum to those infections which cannot be treated effectively with other antibiotic agents. When another agent is as efficacious as Laevomycetinum and potentially less toxic, the other agent should be used. Laevomycetinum is the drug of choice for typhoid fever. Bacterial meningitis caused by *H. influenzae* is effectively treated. Most anaerobic infections respond to Laevomycetinum. Rickettsial diseases and brucellosis can be treated with laevomycetinum; however, tetracyclines are the preferred agents.

Adverse effects: Hypersensitivity reactions can occur. It may inhibit leucopoiesis and erythropoiesis. The most important effect, which may be related to hypersensitivity, is bone marrow depression, resulting in pancytopenia. Dose-dependent, reversible blood dyscrasias may also occur. Superinfections can occur, including oropharyngeal candidiasis and acute staphylococcal enterocolitis. Gastrointestinal upset can occur, and, as with many of the other broad-spectrum antibiotics, the possibility of diarrhea due to superinfection must be differentiated from local irritation effects. **Gray-baby syndrome** - this condition is seen in neonates, especially premature infants, who have been given relatively large doses of laevomycetinum. Cyanosis, respiratory irregularities, vasomotor collapse, abdominal distention, loose green stools, and an ashen-gray color characterize this often fatal syndrome. The condition develops because of the immature hepatic conjugating mechanism and the inadequate mechanism for renal excretion in neonates.

Macrolides and azalides are divided into two generations:

- 1. First generation: Erythromycinum, Oleandomycini phosphas,**
- 2. Second generation: Azithromycinum, Clarithromycinum, Roxithromycinum, Spiramycinum, Djozamicinum, Midecamycinum.**

The macrolide antibiotics (**erythromycinum, azithromycin, and clarithromycin**) are large cyclic lactone ring structures with attached sugars. Erythromycinum, Oleandomycini sulfas, spiramycinum, djozamicinum, midecamycinum are native antibiotics. Azithromycinum, clarithromycinum, roxythromycinum are semisynthetic antibiotics. These group of antibiotics have low toxicity, may penetrate into cell.

They have bacteriostatic type of action predominantly but in high concentrations they have bactericide influence on gram-positive pneumococci, whooping-cough and diphtheria pathogens. They have high activity on gram-positive cocci (streptococci, staphylococci) and intracellular microorganisms (chlamidia, mycoplasma). They can create high concentrations intracellular.

Erythromycinum is a macrolide antibiotic. Erythromycinum is absorbed slowly. Other drugs have good oral bioavailability, but azithromycin absorption is impeded by food. Macrolides distribute to most body tissues, but azithromycin is unique in that the levels achieved in tissues and in phagocytes are considerably higher (tenfold to 100-fold) than those in the plasma. The elimination of erythromycinum (via biliary excretion) and clarithromycin (via hepatic metabolism and urinary excretion of intact drug) is fairly rapid (half-life 2-5 hours). Azithromycin is eliminated slowly (half-life 2-4 days), mainly in the urine as unchanged drug.

Mechanism of action: **Erythromycinum** and other macrolides inhibit bacterial protein synthesis by binding to 50S ribosomal subunits of sensitive microorganisms; they are usually **bacteriostatic** but can be bactericidal in certain situations. Erythromycinum has activity against many species of campylobacter, chlamydia, mycoplasma, legionella, gram-positive cocci, and some gram-negative organisms. The spectrums of activity of azithromycin and clarithromycin are similar but include greater activity against chlamydia, *M. avium* complex, and toxoplasma. Clarithromycinum influences *Helicobacter pylori*. Azithromycinum is more active against *H. influenzae*, *M. catarrhalis* and neisseria, more active than erythromycinum according to gram-negative infections. Resistance to the macrolides in gram-positive organisms involves production of a methylase which adds a methyl group to the ribosomal binding site. Resistance in enterobacteria is the result of formation of drug-metabolizing esterases. Cross-resistance between the individual macrolides is complete. Macrolides blocks translocation of peptidyl-tRNA from the acceptor site to the donor site. Incoming charged tRNA cannot access the occupied acceptor site, so the next amino acid cannot be added to the nascent peptide chain. Macrolides may

also block formation of the initiation complex. Spiramycinum, djozamicinum, midecamycinum influence streptococci resistance to erythromycinum.

Therapeutic uses: Macrolides are useful for patients who are allergic to penicillinum when the infecting organism is sensitive to macrolides, particularly in cases of infection with group A *S. pyogenes* and *S. pneumoniae*, *Corinebacterium diphtheria*. Pneumonia due to *Mycoplasma* organisms is effectively treated. Legionnaires' disease is treated with erythromycinum. Topical erythromycinum preparations are used to treat acne. New macrolides have similar indications for use with some addition of oral uses. Azithromycinum is very active in the treatment of urogenital infections. Clarythromycinum is used in a combined therapy of ulcer diseases.

Adverse effects: Erythromycinum has a very low incidence of serious side effects. Cholestatic hepatitis occurs in adults treated for a week or longer with the estolate form. Hepatitis can also occur with the ethylsuccinate and possibly with the stearate. The hepatitis is uncommon and is reversible. Epigastric distress can occur. A high incidence of thrombophlebitis occurs when erythromycinum is administered intravenously, even when the drug is dissolved in a large fluid volume. Superinfection can occur. Transient deafness has been reported, especially with high doses. The macrolides may cause diarrhea and allergic reactions.

Lincosamides

The lincosamides include lincomycinum and clindomycinum, both of which inhibit protein synthesis. They bind to the 50S ribosomal subunit and block peptide bound formation.

Lincomycinum and clindomycinum have bacteriostatic type of action.

Pharmacokinetics: Though in high concentration may have bactericide influence on gram-positive cocci. They penetrate most tissues including bone. They also concentrate in phagocytic cells, pass through the placental barrier. They are metabolized in liver and is excreted in the urine. If renal function is unpaired the amount of drugs is excreted with feces. **Pharmacodynamics:** They are very active against staphylococci and streptococci and obligate anaerobic pathogens.

Clindomycinum is more active in influence on toxoplasma and *Pl. malariae*.

Therapeutic uses: They are used to treat infections of respiratory organs, urinary tract, anaerobic abdominal infections caused bacteroids. Clindomycinum is also used in ulcer disease. Spiromycinum is also used in toxoplasmosis and gonorrhoea.

Adverse effects: Pseudomembranous colitis can occur, resulting in diarrhoea, abdominal pain, fever, and mucus and blood in the stools. They may cause allergic reactions. This potentially fatal condition, caused by *C. difficile*, can be treated with vancomycinum.

Glycoproteins

Vancomycinum is a bactericidal glycoprotein which binds to the D-Ala-D-Ala terminal of the nascent peptidoglycan pentapeptide side chain and inhibits transglycosylation. This action prevents elongation of the peptidoglycan chain and interferes with cross-linking.

Pharmacokinetics: Vancomycinum is not absorbed from the gastrointestinal tract and may be given orally for bacterial enterocolitis. When given parenterally, vancomycinum penetrates most tissues and is eliminated unchanged in the urine. Dosage modification is mandatory in patients with renal impairment. Fosfomycin is excreted by the kidney, with urinary levels exceeding the **minimal inhibitory concentrations (MICs)** for many urinary tract pathogens.

Pharmacodynamics: Vancomycinum **teicoplaninum** is bacteriostatic against staphylococci, streptococci, and enterococci, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Clostridium perfringens*. Fosfomycinum is an antimetabolite inhibitor of cytosolic enolpyruvate transferase. This action prevents the formation of *N*-acetylmuramic acid, an essential precursor molecule for peptidoglycan chain formation. Resistance to fosfomycin occurs via decreased intracellular accumulation of the drug. Bacitracinum is a peptide antibiotic which interferes with a late stage in cell wall synthesis in gram-positive organisms. Because of its marked nephrotoxicity the drug is limited to topical use.

Advers effects of vancomycinum include chills, fever, trombophlebitis,

ototoxicity, nephrotoxicity, and hypersensitivity. Rapid intravenous infusion may cause diffuse flushing ("red man syndrome").

In a single dose, the drug is less effective than a 7-day course of treatment with fluoroquinolones. With multiple dosing, resistance emerges rapidly and diarrhea is common. Fosfomycin may be synergistic with beta-lactam and quinolone antibiotics in specific infections.

Cycloserinum: Cycloserinum is an antimetabolite which blocks the incorporation of D-Ala into the pentapeptide side chain of the peptidoglycan. Because of its potential neurotoxicity (tremors, seizures, psychosis), Cycloserinum is only used to treat tuberculosis caused by organisms resistant to first-line antituberculous drugs.

Polypeptides

Polymyxins

Pharmacokinetics. **Polymixinum M sulfas** is for orally administration and **Polymyximum B sulfas** is for parenteral administration. They influence gram-negative bactericidity. They are used in case of urinary and intestines infections. They may call allergy, toxic influence on kidney.

Mechanisms: The polymyxins are polypeptides which are bactericidal against gram-negative bacteria. These drugs interact with a specific lipopolysaccharide component of the outer cell membrane which is also a binding site for calcium. Membrane lipid structure is distorted with an increase in permeability to polar molecules, resulting in marked changes in cell metabolism.

Pharmacodynamics: The spectrum of action includes mainly the gram-negative bacteria (*P. aeruginosa*, salmonella, shigella, escherichia coli, pasteurilla, brucella, *H. influenzae* etc.). Gram-positive microorganisms, *Proteus* and *Neisseria* are resistant.

Therapeutic use: Because of toxicity, the clinical applications of the polymyxins are limited to topical therapy of resistant gram-negative infections, including those caused by enterobacter and pseudomonas. These drugs are occasionally administered into infected cavities, the joints and the pleural and

peritoneal cavities.

Adverse effects: If absorbed into the systemic circulation, adverse effects include neurotoxicity (paresthesias, dizziness, ataxia) and acute renal tubular necrosis (hematuria, proteinuria, nitrogen retention).

Other bactericidal antibiotics

Fusidinum natrium has steroid structure, influences gram-positive microorganism (staphylococcus and streptococcus).

Streptogramins are bactericidal for most susceptible organisms. They bind to the 50S ribosomal subunit, constricting the exit channel on the ribosome through which nascent polypeptides are extruded. In addition, transfer RNA (tRNA) synthetase activity is inhibited, leading to a decrease in free tRNA within the cell. Linezolid is mainly bacteriostatic. The drug binds to a unique site on the 50S subunit, inhibiting initiation by blocking formation of the tRNA-ribosome-mRNA ternary complex.

Fosfomicinum is an extended-spectrum antibiotic, effective against both gram-positive, gram-negative micro-organisms, including *P. aeruginosa*, *Proteus mirabilis*.

№	Drug	Drug forms
1.	Benzylopenicillinum-Natrium	Flac. 250000 UA, 500000 UA, 1000000 UA
2.	Bicillinum-1	Flac. 300000 UA, 600000 UA, 1200000 UA
3.	Bicillinum-5	Flac. 1500000 UA
4.	Oxacillinum-Natrium	Flac. 0,25, 0,5; tab. 0,25, 0,5
5.	Ampicillini Trihydras	Tab. 0,25, 0,5
6.	Ampicillinum-Natrium	Flac. 0,25, 0,5
7.	Amoxycillinum	Caps. 0,25, 0,5
8.	Cefaloridinum	Flac. 0,25, 0,5, 1

9.	Cefazolin (Kefzol)	Flac. 0,25, 0,5, 1, 2, 4
10.	Cefataxim (Claforan)	Flac. 0,5, 1, 2
11.	Cefpirom (Keiten)	Flac. 1,0
12.	Ceftriaxonum Natrium	Flac. 1,0
13.	Tienam	Flac. 60ml, 100ml
14.	Asactam	Flac. 0,5, 1; Flac. 15ml, 100ml
15.	Tetracyclinum	Tab. 0,05, 0,1, 0,25
16.	Tetracyclini hydrochloridum	Ung. 10,0; Flac. 0,1; tab. 0,1, 0,25
17.	Methacyclini hydrochloridum	Caps. 0,15, 0,3
18.	Doxycylinum	Tab. 0,5, 0,1
19.	Neomycini sulfas	Ung. 1%, 2% - 15, 30; Flac. 0,5; tab. 0,1, 0,25
20.	Gentamycini sulfas	Flac. 0,08; amp. 4% - 1, 2ml; ung. 0,1% - 10
21.	Erythromycinum	Tab. 0,1 (100000 UA); 0,25 (250000 UA); Caps. 0,1 (100000 UA), 0,2 (200000 UA); Ung. 3, 7, 10, 15, 30 (1,0 – 10000 UA)
22.	Spiramycinum (Rovamycinum)	Tab. 1,5 (3000000 UA); Gran. 1500000 UA, 750000 UA, 375000 UA; Flac. 1500000 UA
23.	Azithromycinum	Tab. 0,5;

		Caps. 0,125, 0,25; Sirupus 0,02, 0,04 – 1ml
24.	Fusidinum-Natrium	Tab. 0,125, 0,25
25.	Lincomycini hydrochloridum	Caps. 0,25; Amp. 30% 1ml, 2ml
26.	Polymyxini M sulfas	Flac. 500000 UA, 1000000 UA; Tab. 500000 UA; Linimentum 30 (1 – 10000)
27.	Polymyxini B sulfas	Flac. 250000 UA, 500000 UA
28.	Rifampicinum	Caps. 0,15, 0,3
29.	Nystatinum	Tab. 500000 UA; Supp. 500000 UA; Ung. 15, 30 (100000 UA– 1,0)
30.	Amphotericinum B	Flac. 50000 UA; ung. 15, 30 (30000 UA– 1,0)
31.	Griseofulvinum	Tab. 0,25; Susp. 100ml; Linimentum 2,5% - 30
32.	Umcalor	Flac. 20, 50ml

AGENTS USED FOR TREATMENT OF FUNGUS INFECTIONS

Antifungal drugs are divided into 1) antibiotics - Amphotericinum B, nystatinum, levorinum, and natamycinum; 2) synthetic agents: azoles – itraconazolum, ketoconazolum, miconazolum, fluconazolum, clotrimazolum, econazolum, variconazolum etc., other drugs – terbinafinum, natrii tetraboras, flucitozinum etc. Most of fungi are resistant to conventional antimicrobial agents and only a few drugs are available for the treatment of systemic fungal diseases. Amphotericinum B and the azoles (fluconazolum, itraconazolum, and ketoconazolum) are useful in systemic infections and are selectively toxic to fungi because they interact with ergosterol or inhibit its synthesis. Ergosterol is a sterol that is unique to the fungal cell membrane;

the predominant sterol of human cells is cholesterol.

A number of antifungal drugs are used topically for superficial infections caused by *C. albicans* and dermatophytes. **Nystatinum** is a polyene antibiotic (related to amphotericinum) which disrupts fungal membranes by binding to ergosterol. Nystatinum is commonly used topically to suppress local *Candida* infections and has been used orally to eradicate gastrointestinal fungi in patients with impaired defense mechanisms. Other topical antifungal agents include the azole compounds **miconazolum** and **clotrimazolum** and the nonazoles **tolnaftatum**, and **undecylenic acid**.

Nystatinum is a polyene antibiotic.

Mechanism of action: The drug is **fungistatic** and **fungicidal**. It binds to sterols, especially ergosterol, which is enriched in the membrane of fungi and yeasts. As a result of this binding, the drug appears to form channels in the membrane which allow small molecules to leak out of the cell.

Pharmacokinetics: Nystatinum is not absorbed appreciably from the gastrointestinal tract. It is not absorbed from the skin or mucous membranes. It is not employed parenterally. It is poorly soluble and decomposes rapidly in water.

Therapeutic uses: Nystatinum is used to treat *Candida* infections of the skin, mucous membranes, and intestinal tract. Thrush (oral candidiasis) and vaginitis are treated by topical application, whereas intestinal candidiasis is treated by oral administration. Nystatinum is supplied as an ointment, oral suspension, oral tablets, drops, and powder.

Adverse effects: Occasional gastrointestinal disturbances occur with oral administration.

Laevorinum is a similar drug which also influences trichomonades.

Amphotericinum B is a polyene antibiotic related to nystatinum. Amphotericinum is poorly absorbed from the gastrointestinal tract and is usually administered intravenously as a colloidal suspension, or in some cases in a lipid formulation. The drug is widely distributed to all tissues except the CNS. Elimination is mainly via slow hepatic metabolism; the half-life is approximately 2 weeks. A small

fraction of the drug is excreted in the urine, dosage modification is necessary only in extreme renal dysfunction. Amphotericin B is not dialyzable.

Mechanism of action: The mechanism of action is the same for amphotericin B as for nystatin. The fungicidal action of amphotericin B is due to its effects on the permeability and transport properties of fungal membranes. Polyenes are molecules with both hydrophilic and lipophilic characteristics, i.e., they are amphipathic. They bind to ergosterol, a sterol specific to fungal cell membranes, and cause the formation of artificial pores. Resistance can occur via a decreased level of – or a structural change in – membrane ergosterol.

Pharmacokinetics. Amphotericin B is absorbed poorly from the gastrointestinal tract. Intravenous administration results in a plasma half-life of about 24 hours. The drug is excreted very slowly in the urine.

Pharmacologic effects: Amphotericin B is a broad-spectrum antifungal agent. *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Candida* species, *Blastomyces dermatitidis*, and some strains of *Aspergillus* and *Sporotrichum* are sensitive. The concentration of amphotericin B determines whether it is fungistatic or fungicidal.

Therapeutic uses: Amphotericin B is the most effective drug available for systemic fungal infections. It is frequently used for the treatment of life-threatening fungal infections in patient with impaired defense mechanisms (e.g. patients undergoing immunosuppressive therapy or cancer chemotherapy, and patients with AIDS). Amphotericin B is used in the treatment of the following infections: pulmonary, cutaneous, and disseminated forms of blastomycosis; acute pulmonary coccidioidomycosis; pulmonary histoplasmosis; *C. neoformans* infections – now the most common life-threatening fungal pathogen associated with AIDS; candidiasis, including disseminated forms. Intrathecal infusion may be helpful in the treatment of fungal meningitis.

Adverse effects: All patients receiving amphotericin B therapy should be hospitalized, at least during the initiation of therapy. Hypersensitivity reactions can occur, including anaphylaxis. Fever, chills, headache, and gastrointestinal

disturbances are common with intravenous administration. Patients usually develop tolerance to these adverse effects with continuing administration of amphotericin B. Decreased renal function occurs in over 80% of patients treated with amphotericin B, necessitating close observation. Normochromic normocytic anemia can occur. Thrombophlebitis can occur.

Griseofulvinum is produced by *Penicillium griseofulvum*.

Mechanism of action: Griseofulvinum binds to polymerized microtubules, disrupting the mitotic spindle. Griseofulvinum interferes with microtubule function in dermatophytes and may also inhibit the synthesis and polymerization of nucleic acids. Sensitive dermatophytes take up the drug by an energy-dependent mechanism, and resistance can occur via decrease in this transport. It is fungistatic.

Pharmacokinetics: Oral absorption of griseofulvinum depends on the physical state of the drug – ultramicrosize formulations, which have finer crystals or particles, are more effectively absorbed—and is aided by high-fat foods. The drug is distributed to the stratum corneum, where it binds to keratin. Biliary excretion is responsible for its elimination. Griseofulvinum is absorbed in the upper part of the small intestine following oral administration. Most of the drug is eliminated unchanged in the feces. Griseofulvinum has a particular affinity for keratin.

Pharmacologic effects: **Griseofulvinum** is active against dermatophytes, including *Microsporum*, *Epidermophyton*, and *Trichophyton* species. It is ineffective against yeasts.

Therapeutic uses: Because of its affinity for keratin, griseofulvinum is useful for treating mycotic diseases of the skin, hair, and nails, such as tinea capitis, pedis (athlete's foot), cruris, corporis, and circinata. It is given orally; topical use has little effect.

Adverse effects: Extensive clinical use of griseofulvinum has revealed relatively low toxicity. Possible side effects include headache, neurologic alterations, hepatotoxicity, leukopenia, neutropenia, gastrointestinal distress, and skin reactions, including urticaria and photosensitivity.

Synthetic antifungal drugs

Flucytosinum

Mechanism of action: Flucytosinum is converted within fungal cells (but not in the host's cells) to 5-fluorouracil, a metabolic antagonist which ultimately leads to inhibition of thymidylate synthetase.

Pharmacokinetics: Flucytosinum is well absorbed from the gastrointestinal tract and is distributed widely throughout the body, including the cerebrospinal fluid. It is excreted in the urine, mainly in an unmetabolized form.

Pharmacologic effects: The drug is effective against *C. neoformans*. It is effective against some strains of *Candida*, including some *Candida albicans* strains. However, *C. albicans* can become resistant to flucytosine during therapy.

Therapeutic uses: Although flucytosine is not as effective as amphotericin B, it is less toxic and can be administered orally. It is used for systemic infections caused by *C. albicans* and *C. neoformans* (*Cryptococcus meningitidis*). It is most often used in combination with amphotericin B. Recently, the value of this combination has been challenged in patients with AIDS having cryptococcal meningitis because of its toxicity.

Adverse effects have included: fatal bone marrow depression, gastrointestinal upset, skin rash, hepatic dysfunction.

Azoles

Classification and pharmacokinetics: The azoles used for systemic mycoses include ketoconazole, fluconazole, itraconazole, and voriconazole. Oral bioavailability is variable (normal gastric acidity is required). Fluconazole and voriconazole are more reliably absorbed via the oral route than the other azoles. The drugs are distributed to most body tissues, but with the exception of fluconazole, drug levels achieved in the CNS are low. Liver metabolism is responsible for the elimination of ketoconazole, itraconazole, and voriconazole. Fluconazole is eliminated by the kidneys, largely in unchanged form.

Mechanism of action: The azoles interfere with fungal cell membrane permeability by inhibiting the synthesis of ergosterol. These drugs act at the step of

14a-demethylation of lanosterol, which is catalyzed by a cytochrome P450 isozyme. With increasing use of azole antifungals, especially for long-term prophylaxis in immunocompromised and neutropenic patients, resistance is occurring, possibly via changes in the sensitivity of the target enzymes.

Therapeutic uses: Ketoconazole has a narrow antifungal spectrum and is considered to be a backup drug for systemic infections caused by certain blastomyces, coccidioides, and histoplasma. Ketoconazole has been used commonly for chronic mucocutaneous candidiasis and when given orally is also effective against dermatophytes. Fluconazole is a drug of choice in esophageal and oropharyngeal candidiasis and for most infections due to coccidioides. A single oral dose usually eradicates vaginal candidiasis. Fluconazole is now the drug of choice for initial and secondary prophylaxis against cryptococcal meningitis and is an alternative drug of choice (with amphotericin B) in treatment of active disease due to *Cryptococcus neoformans*. The drug is also equivalent to amphotericin B in candidemia. Itraconazole is currently the drug of choice for systemic infections due to blastomyces and sporothrix and for subcutaneous chromoblastomycosis. Itraconazole is an alternative agent in the treatment of infections caused by aspergillus, coccidioides, cryptococcus, and histoplasma. In esophageal candidiasis the drug is active against some strains resistant to fluconazole. Itraconazole is also active in dermatophytoses. Voriconazole is a new azole with an even wider spectrum of fungal activity than itraconazole. Its clinical usefulness and toxic potential remain to be established.

Adverse effects: Ketokonazole causes: nausea and vomiting are the most common adverse reactions; hepatotoxicity, hypersensitivity reactions (including urticaria or anaphylaxis), and gynecomastia are less common untoward effects; ketoconazole transiently blocks testosterone synthesis and the adrenal response to corticotrophin; ketoconazole blocks several cytochrome P-450-related enzyme steps and, therefore, has the potential to interact with drugs metabolized by the microsomal enzyme system. Fluconazole is less toxic than amphotericin B or flucytosine and better tolerated than ketoconazole. Fluconazole should be

discontinued in patients with progressive hepatic dysfunction. c. Though it has a lower binding affinity for cytochrome P-450 enzymes than ketoconazole, it may increase serum concentrations of phenytoin, cyclosporine, and oral hypoglycemic drugs and potentiate the effect of warfarin.

Terbinafinum

Mechanism of action: Terbinafinum inhibits a fungal enzyme, squalene epoxidase. It causes accumulation of toxic levels of squalene, which can interfere with ergosterol synthesis. Terbinafinum is fungicidal.

Therapeutic uses and adverse effects: Like griseofulvinum, terbinafinum accumulates in keratin, but it is much more effective than griseofulvinum in onychomycosis. Adverse effects include gastrointestinal upsets, rash, headache, and taste disturbances. terbinafinum does not inhibit cytochrome P450.

Miconazolum and clotrimazolum

These imidazole derivatives are used primarily as topical agents. They inhibit the growth of common dermatophytes and yeasts, including *Trichophyton* species, *Epidermophyton floccosum*, *C. albicans*, and *Malassezia furfur*. They are used for the treatment of ringworm and other skin infections caused by susceptible organisms, and for vulvovaginal candidiasis. Miconazolum is also available for parenteral administration in the treatment of severe systemic fungal infections, such as candidiasis, coccidioidomycosis, and cryptococcosis. However, toxicity and limited efficacy restrict its usefulness.

№	Drug	Drug forms
1.	Amphotericinum B	Flac. 50000 UA; Ung. 15, 30 (1,0 – 30000 UA)
2.	Nystatinum	Tab. 250000 UA, 500000 UA; Supp. 250000 UA, 500000 UA; Ung. 15, 30 (ung. 1,0 – 100000 UA)
3.	Griseofulvinum	Tab. 0,125
4.	Clotrimazolum	Tab. 0,1;

		Cream 1% 20; Flac. 1% - 15ml
5.	Ketokonazolom (Nyzoral)	Tab. 0,2; Cream 2% - 15, 30
6.	Itrakonazolom (Orungal)	Caps. 0,1
7.	Flukonazolom (Diflukan)	Caps. 0,05, 0,1, 0,15
8.	Terbinafinum (Lamisil)	Tab. 0,25; Cream 1% - 15,0; Flac. 1% - 30ml; Aerosol 1% - 30ml

Sulfonamides

The sulfonamides are derivatives of **sulfanilamide**. Derivatives are made by substitutions in the amide of the sulfonamide group. The Sulfonamides are weakly acidic compounds which have a common chemical nucleus resembling *p*-aminobenzoic acid (PABA). Members of this group differ mainly in their pharmacokinetic properties and clinical uses. Pharmacokinetic features include modest tissue penetration, hepatic metabolism, and excretion of both intact drug and acetylated metabolites in the urine. Solubility may be decreased in acidic urine, resulting in precipitation of the drug or its metabolites. The sulfonamides is classified by pharmacokinetics:

I. Sulfonamides which are resorted,

1. Sulfonamides of short action: sulfadimezinum and aethazolom.
2. Sulfonamides of long action: sulfadimethoxinum and sulfapyridazinum.
3. Drugs with ultralong action: sulfalenum.

II. Drugs which are not absorbed: Phthalazolom, Phthazinum, and Sulginum.

III. Drugs for local action: Sulfacylum-natrium, Aethazolom, and Argosulphanum.

IV. Combination therapy: Biseptolum (Co-trimoxazolom).

Mechanism of action: Sulfonamides prevent the incorporation of para-aminobenzoic acid (PABA) into folic acid, which in the reduced form is necessary in purine biosynthesis for the transfer of one-carbon units. Susceptible bacteria are those which need PABA because they are incapable of using folic acid directly. Human cells use exogenous folic acid exclusively, and thus, a lack of PABA does not affect them. They can also act as substrates for this enzyme, resulting in the synthesis of nonfunctional forms of folic acid.

Trimethoprim - this drug is structurally similar to folic acid. It is a weak base and is trapped in acidic environments, reaching high concentrations in prostatic and vaginal fluids. It is a selective inhibitor of bacterial dihydrofolate reductase which prevents formation of the active tetrahydroform of folic acid.

Trimethoprim plus sulfamethoxazole. Trimethoprim is a highly selective inhibitor of the dihydrofolate reductase of lower organisms. The combination is useful for treating *Pneumocystis carinii* pneumonia, an opportunistic infection seen in patients with AIDS.

When the two drugs are used in combination, antimicrobial synergy results from the **sequential blockade** of foliate synthesis. The drug combination is bactericidal against susceptible organisms.

Pharmacokinetics: Sulfonamides are absorbed within minutes following oral administration. They conjugate with plasma proteins and duration of their action depends on the stability of this connection. They are distributed throughout the body water. They diffuse into cerebrospinal fluid. They are metabolized by acetylation of the para-NH₂, which negates the antibacterial activity but not the unwanted effects, sulfadimethoxinum is conjugated with glucuronic acid. Excretion is chiefly via the urine within. The urinary solubility of the various sulfonamides and duration of action varies widely.

A large fraction of trimethoprim is excreted unchanged in the urine. The half-life of this drug is similar to that of sulfamethoxazole (10-12 hours).

Pharmacologic effects: Sulfonamides are effective against many gram-positive bacteria, including group A *Streptococcus pyogenes* and *Streptococcus pneumoniae*.

Many gram-negative bacteria are resistant to sulfonamides, but some, such as *Hemophilus influenzae*, *Escherichia coli* (the organism most often suspect in acute urinary tract infections), *Shigella*, *Yersinia enterocolitica*, and *Proteus mirabilis*, often are sensitive. Other susceptible organisms include *Bacillus anthracis*, *Nocardia*, *Actinomyces*, and *Chlamydia trachomatis*, the agent responsible for trachoma, lymphogranuloma venereum, and inclusion conjunctivitis.

Therapeutic uses: Sulfonamides are the preferred agents for treatment of: acute uncomplicated infections of breathing system, urinary tract infections; nocardiosis. It is used in otholaryngology. They are effective for treatment of malaria, toxoplasmosis when used in combination with pyrimethaminum, malarial with specific antimalarial drugs. They are used in trachoma and inclusion conjunctivitis as an alternative to tetracycline.

Sulfadimezinum is rapidly absorbed and rapidly undergoes urinary excretion. Sulfadimezinum is now used less often for urinary tract infections. It is useful for treating diseases of breathing system nocardiosis.

Long acting sulphonamides (sulfapyridazinum, sulfadimethoxinum) are rapidly absorbed, slowly excreted. Period of half-excretion 24-48h. Ultra-long action sulfalenum has period of half excretion less than 48 hours.

Biseptolum has wider spectrum of action. The combination was designed to delay development of bacterial resistents. Biseptolum is used for treatment of genitourinary, gastromtestinal, respiratory tract infections. **Sulfacylum natrium** is used in case of infections of the eyes. **Phthalazolium** is unabsorbed in the gastromtestinal tract following oral administration, produces changes only on local gut bacteria flora and finds wide use in presurgical bowel sterilization and in treatment of intraabdominal infections.

Adverse effects: About 75% of untoward effects involve the skin with sensitization often being responsible. Conditions produced include: exfoliative dermatitis; Stevens-Johnson syndrome (fever, malaise, and erythema multiforme). Drug fever can occur and is probably due to sensitization. Blood dyscrasias are rare but can occur. Sulfonamidetherapy is stopped immediately if any of the following

hematologic conditions develop to a serious extent: acute hemolytic anemia, which is often, but not solely, due to an erythrocytic deficiency of glucose-6-phosphate dehydrogenase activity and is particularly likely to develop in blacks and children; aplastic anemia; agranulocytosis; thrombocytopenia. Eosinophilia may accompany other manifestations of hypersensitivity. Crystalluria is a condition which was seen with the older sulfonamides but rarely occurs with the newer, more soluble agents such as sulfisoxazole, although some renal damage is still possible. Hepatitis, causing focal or diffuse necrosis of the liver, occurs rarely and may be caused by either direct drug toxicity or sensitization. Kernicterus can occur in the newborn because of displacement of bilirubin from plasma albumin.

Quinolones

There are **quinolons of first generation** – nitroxolinum, which influence gram-positive, gram-negative microorganisms, fungus (complex with ferum ions, disturb oxidative-reductive process). It is used in urological diseases.

Adverse effects: allergy, dyspepsia.

There are **quinolons of second generation**. This quinolone drug acts against many gram-negative organisms (but not proteus or pseudomonas) by mechanisms which may involve acidification or inhibition of the DNA gyrase. Resistance emerges rapidly. The drug is active orally and is excreted in the urine partly unchanged and partly as the inactive glucuronide. Toxic effects include gastrointestinal irritation, glycosuria, skin rashes, phototoxicity, visual disturbances, and the CNS stimulation. Acidum nalidixicum influences gram-negative microorganisms, disturbs nucleic metabolisms and is used in urinary diseases.

Adverse effects: allergy, dyspepsia, and headache.

There are quinolones of third generation: **ofloxacinum, ciprofloxacinum, pefloxacinum, norfloxacinum, fleroxacinum, enoxacinum, gatifloxacinum, levofloxacinum, lomefloxacinum, and sparfloxacinum**. All of the drugs have good oral bioavailability (antacids may interfere) and penetrate most body tissues. However, norfloxacinum does not achieve adequate plasma levels for use in most systemic infections. Elimination of most fluoroquinolones is through the kidneys via active tubular

secretion (which can be blocked by probenecid). Dosage reductions are usually needed in renal dysfunction. Moxifloxacinum, sparfloxacinum, and trovafloxacinum are eliminated partly by hepatic metabolism and also by biliary excretion. Half-lives of fluoroquinolones are usually in the range of 3-8 hours, but the drugs eliminated by nonrenal routes have half-lives in the 10- to 20-hour range.

Mechanism of action: The fluoroquinolones interfere with bacterial DNA synthesis by inhibiting topoisomerase II (DNA gyrase) and topoisomerase IV. They block the relaxation of supercoiled DNA which is catalyzed by DNA gyrase – a step required for normal transcription and duplication. Inhibition of topoisomerase IV by fluoroquinolones interferes with the separation of replicated chromosomal DNA during cell division. Fluoroquinolones are usually bactericidal against susceptible organisms. The quinolones act on DNA gyrase, an enzyme involved in DNA replication. They are rapidly bactericidal. Resistance to the fluoroquinolones does not develop rapidly as it does with nalidixic acid.

Pharmacokinetics: Ofloxacinum, norfloxacinum and ciprofloxacinum are rapidly absorbed when given orally. Their serum elimination half-life is 3-4 hours. The drugs are metabolized in the liver to some extent. They are excreted in the urine via glomerular filtration and tubular secretion. The drugs are widely distributed throughout the body, but concentrations in the cerebrospinal fluid are low.

Pharmacologic effects: Fluoroquinolones are active against many gram-positive and gram-negative bacteria. Additionally, ciprofloxacinum, ofloxacinum, lomefloxacinum are active against some mycobacteria tuberculosis. They are highly active against gonococci, are active against virtually all urinary tract pathogens. They are highly active against bacteria which cause enteritis and against staphylococci, including strains resistant to methicillinum. But they are somewhat less active against *P. aeruginosa* and many streptococci, and they have poor activity against anaerobes.

Therapeutic uses: Fluoroquinolones are indicated for complicated and uncomplicated urinary tract infections, for serious infectious diarrhea; for infections of bones, joints, skin, and soft tissue; and for lower respiratory tract infections, including those in patients with cystic fibrosis.

Adverse effects: Dyspepsia, headache, skin allergy. Quinolones can cause arthropathy in young animals and, therefore, they are not used in patients under age 17, during pregnancy, or in nursing mothers. Crystalluria has occurred rarely, particularly with alkaline urine. Fluoroquinolones are inhibitors of gamma-aminobutyric acid (GABA) and may cause seizures.

№	Drug	Drug forms
1.	Sulfadimezinum	Pulv.; Tab. 0,25, 0,5
2.	Aethazolum	Pulv.; Tab. 0,25, 0,5
3.	Sulfadimethoxinum	Pulv.; Tab. 0,2, 0,5
4.	Phthalazolum	Pulv.; Tab. 0,5
5.	Sulfapyridazinum	Pulv.; Tab. 0,5
6.	Sulfalenum	Tab. 0,2
7.	Sulfacylum- Natrium	Amp. 30% - 5ml; Guttas 20%, 30% - 1,5ml; Ung. 30% - 10,0
8.	Bactrim (Biseptolum-480)	Tab. № 20
9.	Acidum Nalidixicum	Tab. 0,5; Caps. 0,5
10.	Nitroxolinum	Tab. 0,05; Dragee 0,05
11.	Ofloxacinum	Tab. 0,2
12.	Ciprofloxacinum	Tab. 0,25, 0,5, 0,75; Flac. 0,2% - 50, 100ml;

		amp. 1% - 10ml
13.	Furazolidonum	Tab. 0,05
14.	Furadoninum	Tab. 0,05, 0,1
15.	Nifuroxazidum	Tab. 0,1

AGENTS USED FOR TREATMENT OF TUBERCULOSIS

The incidence of tuberculosis has been increasing because the disease can occur in patients with AIDS. Drugs are used in combination because otherwise microbial resistance rapidly develops. All the drugs according to their effectiveness are divided into three groups:

- 1. Group A (the most effective):** Rifampicinum, Isoniazidumum and other derivatives of hydrozyde of isonicotinic acids.
- 2. Group B (less effective than group A):** Streptomycini sulfas, Kanamycinumum, Florymycini sulfas, Cycloserinum, Amikacinumum, Acthinamidum, Protonamidum, Pyrazinamidum, Ethambutolumum, Ofloxacinumum, Lomefloxacinumum, and Moxifloxacinum.
- 3. Group C (less effective than group B):** Natrii paraaminosalicylas, Thiosemi carbazonum.

The chemotherapy of infections caused by *Mycobacterium tuberculosis*, *M leprae*, and *M avium-intracellulare* is complicated by numerous factors, including limited information about the mechanisms of antimycobacterial drug actions; the development of resistance; the intracellular location of mycobacteria; and the chronic nature of mycobacterial disease, which requires protracted drug treatment and is associated with drug toxicities. Chemotherapy of mycobacterial infections almost always involves the use of drug combinations to delay the emergence of resistance and to enhance antimycobacterial efficacy. The major drugs used in tuberculosis are isoniazidum (INH), rifampicinum, ethambutolum, pyrazinamidum. Actions of these agents on *M tuberculosis* are bactericidal or bacteriostatic depending on drug concentration and strain susceptibility. Suppression of *M avium-intracellulare* in the immunocompromised patient also requires multidrug treatment. The primary drug

for leprosy is dapsonum, commonly given with rifampicinum or clofaziminum (or both).

Isoniazidum is the hydrazide of isonicotinic acid and is a pyridine.

Mechanism of action: Isoniazidum probably interferes with cellular metabolism, especially the synthesis of mycolic acid, an important constituent of the mycobacterial cell wall. Isoniazidum (INH) is a structural congener of pyridoxine. Its mechanism of action involves inhibition of enzymes required for the synthesis of mycolic acids and mycobacterial cell walls. It can inhibit nucleic metabolism and compete with vitamins B1, B3, B6. Resistance can emerge rapidly if the drug is used alone.

Pharmacokinetics: The drug is well absorbed from the gastrointestinal tract and diffuses readily into all body tissues and body fluids, including cerebrospinal fluid. The plasma concentration and the metabolism of isoniazidum are affected by whether a given patient is a fast or a slow acetylator of the drug, a genetically determined trait. Isoniazidum is excreted mainly in the urine. Slow acetylators have a higher concentration of unchanged or free isoniazidum than fast acetylators. The liver metabolism of isoniazidum is by acetylation and is under genetic control. Patients may be fast or slow inactivators of the drug.

Pharmacologic effects: Isoniazidum is effective against most tubercle bacilli. It is not effective against many atypical mycobacteria. To prevent mycobacterial resistance, isoniazidum is used in conjunction with other agents.

Therapeutic uses: Isoniazidum is the most widely used agent in the treatment and prophylaxis of tuberculosis.

Adverse effects: Up to 20% of patients taking isoniazidum develop elevated serum aminotransferase levels. Severe hepatic injury occurs more frequently in patients over the age of 35, especially in those who drink alcohol daily. Isoniazidum is discontinued if symptoms of hepatitis develop or if the aminotransferase activity increases to more than three times normal. Peripheral and the CNS toxicity occur. This toxicity probably results from an increased excretion of pyridoxine induced by isoniazidum, which produces a pyridoxine deficiency. Peripheral neuritis, urinary

retention, insomnia, and psychotic episodes can occur. Concurrent pyridoxine administration with isoniazidum prevents most of these complications. Isoniazidum can also exacerbate pyridoxine-deficiency anemia and can produce blood dyscrasias. Hypersensitivity reactions (i.e., fever, various rashes) can occur.

Rifampicin belongs to the group of complex macrocyclic antibiotics.

Mechanism of action: Rifampicin inhibits RNA synthesis in bacteria and chlamydiae by binding to DNA-dependent RNA polymerase. Rifampicin – a derivative of rifamycin – is bactericidal against *M tuberculosis*. The drug inhibits DNA-dependent RNA polymerase (encoded by the *rpo* gene) in *M tuberculosis* and many other microorganisms. Resistance via changes in drug sensitivity of the polymerase emerges rapidly if the drug is used alone.

Pharmacokinetics: When given orally, rifampicin is well absorbed and is distributed to most body tissues, including the CNS. The drug undergoes enterohepatic cycling and is partially metabolized in the liver. Both free drug and metabolites (which are orange-colored) are eliminated mainly in the feces. Rifampicin is well absorbed from the gastrointestinal tract. It is widely distributed in tissues and is excreted mainly through the liver.

Pharmacologic effects: Most gram-positive and many gram-negative microorganisms are sensitive to rifampicin. Prolonged administration of the drug as the single therapeutic agent promotes the emergence of highly resistant organisms.

Therapeutic uses: Rifampicin is used in the treatment of: tuberculosis (in combination with other agents, often isoniazidum, pyrazinamidum, or ethambutolum); atypical mycobacterial infections; leprosy. Rifampicin is not used for minor infections because of the emergence of rifampicin-resistant bacteria.

Adverse effects: Urine, sweat, tears, and contact lenses may take on an orange color because of rifampicin administration; this effect is harmless. Light-chain proteinuria and impaired antibody response may occur. Rifampicin induces hepatic microsomal enzymes and, therefore, affects the half-life of a number of drugs. For example, a decrease in the effect of some anticoagulants and increased metabolism of methadone occur when these agents are administered concomitantly

with rifampicin. Rashes, gastrointestinal disturbances, and renal damage have been reported. Jaundice and severe hepatic dysfunction are occasionally produced.

There are semisynthetic drugs – rifabutin, etc.

Pyrazinamidum is the pyrazine analogue of nicotinamide.

Mechanism of action: The mechanism of action of pyrazinamidum is not known; however, its bacteriostatic action appears to require metabolic conversion via pyrazinamidases (encoded by the *pncA* gene) present in *M tuberculosis* involve inhibition of oxygen dependent mycolic acid synthesis. Resistant mycobacteria lack these enzymes, and resistance develops rapidly if the drug is used alone. There is minimal cross-resistance with other antimycobacterial drugs. Ethionamidum and protionamidum are less effective.

Pharmacokinetics: Pyrazinamidum is distributed throughout the body after oral administration. It is excreted mainly by glomerular filtration. Pyrazinamidum is well absorbed orally and penetrates most body tissues, including the CNS. The drug is partly metabolized to pyrazinoic acid, and both parent molecule and metabolite are excreted in the urine. The plasma half-life of pyrazinamidum is increased in hepatic or renal failure.

Therapeutic uses: Pyrazinamidum is now widely used in multiagent short-term therapy of uncomplicated pulmonary tuberculosis.

Adverse effects: Liver function studies are performed before and during therapy, because liver damage can occur. Hyperuricemia and gout can occur.

Ethambutolum is derivative of ethylenimine.

Mechanism of action connected with blocking nucleonic acids synthesis. Resistance to the drug occurs rapidly when it is used alone.

Pharmacokinetics: Ethambutolum is well absorbed from the gastrointestinal tract. It is widely distributed in the body, including the cerebrospinal fluid. Most of an ingested dose is excreted unchanged in urine and feces. Ethambutolum inhibits arabinosyl transferases (encoded by the *embCAB* operon) involved in the synthesis of arabinogalactan, a component of mycobacterial cell walls. Resistance occurs rapidly via mutations in the *emb* gene if the drug is used alone. The drug is well

absorbed orally and distributed to most tissues, including the CNS. A large fraction is eliminated unchanged in the urine. Dose reduction is necessary in renal failure.

Pharmacologic effects and therapeutic use: Ethambutolum inhibits many strains of *M. tuberculosis*. It is used in combination with other agents for the treatment of tuberculosis.

Adverse effects: Visual disturbances, including optic neuritis and red-green color-blindness, can occur but are reversible. Hypersensitivity occurs occasionally, resulting in rash or drug fever.

The use of **streptomycinum** in the treatment of tuberculosis has been declining ever since more effective agents became available. When a three-agent combination is used to treat severe forms of tuberculosis (e.g. disseminated or meningeal), streptomycinum may be one of the drugs used seldom. This aminoglycoside is now used more frequently than hitherto because of the growing prevalence of drug-resistant strains of *M tuberculosis*. Streptomycinum is used principally in drug combinations for the treatment of life-threatening tuberculous disease, including meningitis, miliary dissemination, and severe organ tuberculosis. The pharmacodynamic and pharmacokinetic properties of streptomycinum are similar to those of other aminoglycosides. The second-line antimycobacterial drugs are used in cases which are resistant to first-line agents; they are considered second-line drugs because they are no more effective, and their toxicities are often more serious than those of the major drugs.

Amikacinum is indicated for treatment of tuberculosis suspected to be caused by streptomycinum-resistant or multidrug-resistant mycobacterial strains. To avoid emergence of resistance, amikacinum should always be used in combination drug regimens.

Ciprofloxacinum and ofloxacinum are often active against strains of *M tuberculosis* resistant to first-line agents. The fluoroquinolones should always be used in combination regimens with two or more other active agents.

Natrii para-aminosalicylas is now rarely used because primary resistance is common. In addition, its toxicity includes gastrointestinal irritation, peptic ulceration, hypersensitivity reactions, and effects on kidney, liver, and thyroid function. Other drugs

of limited use because of their toxicity include **capreomycinum** (ototoxicity, renal disfunction) and **cycloserinum** (peripheral neuropathy CNS disfunction).

№	Drugs	Drug forms
1.	Isoniazidum	Pulv.; Tab. 0,1, 0,3
2.	Rifampicinum	Caps. 0,05, 0,15
3.	Ethambutolum	Tab. 0,1, 0,2, 0,4
4.	Pirazinamidum	Tab. 0,5
5.	Cycloserinum	Tab., caps. 0,25
6.	Natrii Paraaminosalicylas	Pulv.; Tab. 0,5; Flac. 3% - 250ml

AGENTS USED FOR TREATMENT OF PROTOZOAL INFECTIONS AND MALARIA

Metronidazolum

This drug is very active in protozoal infections, including trichomoniasis, *Giardia lamblia* infestation, and *E. histolytica* amebiasis. It is also effective in the treatment of anaerobic bacterial infections (e.g. caused by *Bacteroides* species).

A disulfiram-like (Antabuse-like) reaction can occur when metronidazolum is taken in combination with an alcoholic beverage. Metronidazolum has 5 nitro-groups which are reduced by microorganisms' enzymes. The enzyme pyruvate-ferrodoxine oxyreductase is founded only in anaerobic organism reduces metronidazolum and thereby activates the drug. Reduced metronidazolum disrupts replication and transcription and inhibits DNA repair.

Pharmacokinetics: Drug's absorption from intestinal tract is usually good. The drug is distributed body fluids, high levels are found in plasma and cerebrovascular fluid. Less than 20% binds to plasma proteins. Metronidazolum is metabolized by oxidation and glucuronide formation in liver and is primarily excreted by kidney, small amounts is found in saliva and milk.

Therapeutic uses: Metronidazolium is used in treatment lyambliosis, trichomoniasis, against intestinal and extraintestinal cysts and trophozoites, anaerobic bacterial infections, cutaneous leishmaniasis.

Adverse effects: dyspepsia, itches, headache.

Tinidazolium is used only orally, is not indicated in leishmaniasis. For treatment of lymbleosis furazolidonum and aminochinololum can be used. For treatment of toxoplasmosis chloridinum and sulfonamides can be used. For treatment of amebiasis there are metronidazolium and tinidazolium if amebas have different localizations. If amebas are localised in the intestines wall and out intestines emetine hydrochloridum is used. When amebas are localized into intestines tetracyclinum is used. If amebas are out of intestines chingaminum is used. Ornidazolium is more active then metronidazolium and tinidazolium for protosoal infections treatment.

№	Drug	Drug forms
1.	Chingaminum	Pulv., tab. 0,25; Amp. 5% - 5ml
2.	Chloridinum	Pulv. , tab. 0,005, 0,01, 0,025
3.	Primachinum	Tab. 0,003, 0,009
4.	Chinini hydrochloridum	Tab. 0,5; 0,25; Amp. 50% - 1ml
5.	Bigumalum	Tab., dragee 0,1; Tab., dragee 0,05
6.	Metronidazolium	Tab. 0,25, 0,5; Supp. 0,5
7.	Tinidazolium	Tab. 0,5
8.	Emetini hydrochloridum	Pulv., amp. 1% - 1ml
9.	Solusurminum	Amp. 20% - 10ml
10.	Aminochinololum	Pulv., tab. 0,05, 0,025

AGENTS USED FOR TREATMENT OF VIRUS INFECTIONS

Viruses are obligate intracellular parasites which require the active

participation of the metabolic processes of the invaded cell to survive. Thus, agents which are able to kill viruses often injure host cells as well. Most clinically useful antiviral agents exert their actions on viral replication, either at the stage of nucleic acid synthesis or the stage of late protein synthesis and processing. Most of the drugs active against herpes viruses and against the human immunodeficiency virus (HTV) are antimetabolites, structurally similar to naturally occurring compounds. In order to interfere with viral nucleic acid synthesis or the late synthesis of viral proteins, antimetabolites must first undergo conversion to active forms, usually triphosphate derivatives.

1. Drugs which influence adsorption and penetration of virus into the cells: Gamma globulin, midantanum, remantadinum.

2. Drugs influence virus deproteinisation: midantanum, remantadinum.

Midantanum and remantadinum inhibit the first steps in replication of the influenza A and rubella viruses. These steps involve viral adsorption to the host cell membrane, penetration into the cell via endocytosis, and viral particle uncapping. The inhibitory action of these drugs may be due to their alkaline reaction, which raises the endosomal pH. At low concentrations, midantanum also binds to a specific protein in the surface coat of the influenza virus to prevent fusion. Drug-resistant influenza A virus mutants can emerge and infect contacts of patients in treatment. Midantanum is a synthetic tricyclic amine with a structure unrelated to that of any other antimicrobial agent.

Mechanism of action: Midantanum, remantadinum may block either the assembly of influenza A virus or the release of viral nucleic acid in the host cell.

Pharmacokinetics: This drug is well absorbed from the gastrointestinal tract, it is not metabolized, and is excreted via the kidney.

Therapeutic uses: Antiviral use. The major anti-infective use for midantanum, remantadinum is for prophylaxis during influenza A virus epidemics at which time unvaccinated patients of all ages who are at high risk are advised to receive the drug. Midantanum, remantadinum does not alter the immune response to influenza A vaccine; thus, vaccination can be given concurrently with the drug. Midantanum,

remantadinum can help to protect immunodeficient patients and those on dialysis/who may have a poor antibody response to the vaccine. Midantanum, remantadinum may also be useful in shortening the duration of symptoms when administered after the onset of illness.

Adverse effects midantanum is dose-related and include confusion, hallucinations, seizures, and coma. Remantadinum has insomnia, disturbances of speech, afaxia.

3. Drugs which influence nucleic metabolism:

Drugs for influenza treatment.

Oseltamivir and Zanamivir

These drugs are inhibitors of neuraminidase produced by influenza influenza A and B. This viral enzyme cleaves sialic acid residues from viral proteins and surface proteins of infected cells, preventing clumping of newly released virions and sticking to cells which are already infected. By preventing these actions, neuraminidase inhibitors impede viral spread. Decreased susceptibility to the drugs is associated with mutations in viral neuraminidase.

Therapeutic uses and adverse effects: Oseltamivir is a prodrug used orally, activated in the gut and the liver. Zanamivir is administered intranasally. The drugs decrease the time to alleviation of influenza symptoms by a day or so and are more effective if used within 24 hours after onset of symptoms.

Drugs with wide spectrum of action.

Vidarabinum is an adenine analogue and has activity against HSV, VZV, and CMV. Its use for systemic infections is limited by rapid metabolic inactivation and by marked toxic potential. However, it has been used intravenously for severe HSV infections, including those resistant to acyclovir, and it also prevents the dissemination of varicella-zoster virus in immunocompromised patients. Vidarabinum is used topically for herpes keratitis, but it has no effect on genital lesions. Toxic effects with systemic use include gastrointestinal irritation, paresthesias, tremor, convulsions, and hepatic dysfunction. Vidarabinum is teratogenic in animals.

Mechanism of action: Vidarabine acts by inhibiting viral DNA polymerase. Mammalian DNA synthesis is affected to a lesser extent.

Therapeutic uses: Vidarabine is used in the treatment of serious herpes simplex infections, including encephalitis, keratoconjunctivitis, and neonatal infections. It is also effective in the treatment of herpes zoster and varicella infections in immunocompromised patients.

Adverse effects. Gastrointestinal disturbances and dose-related CNS toxicity are relatively infrequent. Vidarabine may be carcinogenic and should not be used to treat insignificant infections.

Ribavirin is a synthetic purine nucleoside analogue.

Although the precise antiviral mechanism of ribavirin is not known, the drug inhibits guanosine triphosphate formation, prevents capping of viral mRNA, and can block RNA-dependent RNA polymerases. Ribavirin is used in aerosol form for respiratory syncytial virus infections. Early intravenous administration decreases mortality in Lassa fever and other viral hemorrhagic fevers. Ribavirin has recently been shown to have efficacy in treatment of hepatitis C viral infections. Aerosol ribavirin may cause conjunctival or bronchial irritation. Systemic use results in dose-dependent myelosuppression. Ribavirin is a known human teratogen, absolutely contraindicated in pregnancy.

Mechanism of action: This appears to be multiple: ribavirin monophosphate inhibits enzymes needed for the synthesis of guanine nucleotides; ribavirin triphosphate inhibits viral RNA polymerase by competing for substrate sites; the triphosphate also interferes with the formation of viral messenger RNA.

Pharmacologic effects: Ribavirin is active in vitro against several DNA and RNA viruses, including herpes simplex, influenza A and B, and respiratory syncytial virus (RSV). High concentrations inhibit replication of the virus which causes AIDS.

Therapeutic uses and administration: Ribavirin in aerosol form may decrease morbidity from severe RSV infection in infants and young children. It must be administered via a specific small-particle aerosol generator.

Adverse effects: Ribavirin is contraindicated for patients requiring

mechanical ventilation because the small aerosol particles precipitate on the respirator valves and tubing, causing malfunction which can be lethal. Rash and conjunctivitis occur with aerosol use. Ribavirin is mutagenic, teratogenic, and possibly carcinogenic.

Drugs for herpes infection treatment

Idoxuridinum resembles thymidine in structure, being a halogenated pyrimidine.

Mechanism of action: Idoxuridinum is incorporated into both viral and mammalian DNA, producing DNA which is more susceptible to breakage, and ultimately causing production of altered proteins.

Therapeutic uses: Idoxuridinum is used in the treatment of herpes simplex keratitis. Herpes simplex virus type 2 does not respond to idoxuridinum.

Adverse effects: The drug may cause ocular itching, painful irritation, and photophobia.

Acyclovir is a synthetic purine nucleoside analogue with an acyclic side chain.

Mechanism of action: After being converted in vivo to the triphosphate form, acyclovir inhibits herpes virus DNA synthesis by two means. It interferes with viral DNA polymerase and inhibits viral DNA replication. It is incorporated into DNA and leads to premature chain termination. The drug is several hundred times more toxic for the herpes viruses than for mammalian cells due to an enhanced affinity of the viral enzyme thymidine kinase for acyclovir.

Pharmacologic effects: Acyclovir has inhibitory activity in vitro against herpes simplex virus types 1 and 2, varicella-zoster virus, Epstein-Barr virus, and cytomegalovirus.

Therapeutic uses: The drug is indicated for primary and recurrent mucocutaneous herpes simplex infections in immunocompromised patients. It is also useful in herpes genitalis infections. Oral therapy can shorten the duration of initial genital herpes infections, but it does not cure genital herpes. It is only marginally effective for the treatment of recurrent episodes. Infections recur when the drug is stopped. If taken continuously, oral acyclovir can decrease the frequency of

recurrences, but such use should be limited to those patients with severe recurrences.

Adverse effects: Topical applications can cause local discomfort and pruritus. With oral therapy, nausea, vomiting, diarrhea, and headache are the most common unwanted effects. Intravenous therapy can cause nephrotoxicity, neurologic reactions, local phlebitis, rash, and hives. Orally, acyclovir is well tolerated. Intravenously, encephalopathy develops in 1 % of patients.

Ganciclovir is a synthetic nucleoside analogue of 2'-deoxyguanosine.

Mechanism of action: Ganciclovir inhibits viral DNA synthesis in a manner much like that of acyclovir.

Pharmacologic effects: Ganciclovir inhibits replication of herpes simplex virus types 1 and 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus. Ganciclovir is more active against cytomegalovirus, in vitro, than is acyclovir, but resistant strains can develop.

Therapeutic uses: Ganciclovir is indicated for the treatment of cytomegalovirus retinitis in immunocompromised individuals, including patients with AIDS. However, relapse is common, even with continued treatment.

Adverse effects: When administered intramuscularly or subcutaneously, ganciclovir may cause severe tissue irritation. Granulocytopenia occurs in 40% and thrombocytopenia in 20% of patients treated. These are generally reversible on discontinuation of treatment. The CNS effects, from headache to psychosis, convulsions, or coma, can occur in 5%-15% of patients. Anemia, fever, rash, and abnormal liver function values can occur. Ganciclovir is teratogenic and mutagenic in animals.

Agents of natural origin

Interferons are glycoproteins produced in human leukocytes (IFN- α), fibroblasts (IFN- β), and immune cells (IFN- γ). They increase the stability of macroorganism's cells to virusis. They exert multiple actions which affect viral RNA and DNA synthesis. Interferons induce the formation of enzymes, including a protein kinase which phosphorylates a factor which blocks peptide chain initiation, a phosphodiesterase which degrades terminal nucleotides of tRNA, and enzymes which

activate RNase.

Therapeutic uses and adverse effects: Interferon alpha is approved for use in chronic hepatitis A and B infections, Kaposi's sarcoma, papillomatosis, and topically for genital warts. Another possible use of interferons is to prevent herpes zoster virus dissemination in cancer patients.

Adverse effects include dose-limiting neutropenia, gastrointestinal irritation, fatigue, myalgia, mental confusion, and a reversible cardiomyopathy.

№	Drug	Drug forms
1.	Remantadinum	Tab. 0,05
2.	Oxolinum	Ung. 0,25%, 0,5%, 1%, 2%, 3%
3.	Acyclovirum	Caps. 0,2; Ung. 5%; Flac. 0,25
4.	Interferonum Leucocyticum Humanum Siccum	Pulv. In ampull. 1000 IU – 2ml
5.	Azidothymidinum	Caps. 0,1

ANTI-HIV AGENTS

Anti-HIV agents are divided in two groups: 1) **nucleoside reverse transcriptase inhibitors (nrtis)** and 2) **protease inhibitors**.

Nucleoside reverse transcriptase inhibitors (nrtis)

Zidovudinum

Mechanisms of action: Formerly called azidothymidine (AZT), zidovudinum is a nucleoside requiring phosphorylation by host cell kinases to form a nucleotide analogue which both inhibits reverse transcriptase of HIV-1 and HIV-2 and causes chain termination in viral DNA. Resistance – common in patients with advanced HIV infection – is due to mutations at several sites on the *pol* gene which encodes for several proteins, including reverse transcriptase.

Pharmacokinetics: Zidovudinum is active orally (with 60% bioavailability)

and is distributed to most tissues, including the CNS. Elimination of the drug involves both hepatic metabolism to glucuronides and renal excretion. Dosage reduction is necessary in uremic patients and those with cirrhosis. The half-life of zidovudine is 1-3 hours.

Therapeutic use: Zidovudine continues to be the most frequently used reverse transcriptase inhibitor in combination drug regimens (HAART). It is of value also in prophylaxis against HIV infection through accidental needlesticks and in prophylaxis against vertical transmission from mother to neonate.

Adverse effects: The primary toxicity is bone marrow suppression leading to anemia and neutropenia, which may require transfusions. Bone marrow toxicity is additive with other myelosuppressants. Gastrointestinal distress, thrombocytopenia, headaches, myalgia, acute cholestatic hepatitis, agitation, and insomnia may also occur.

Didanosine

Mechanisms of action: Didanosine is an analogue of deoxyadenosine which is activated by host cell kinases to a triphosphate form which inhibits reverse transcriptase and causes chain termination. Resistant strains are associated with point mutations of the *pol* gene, and there is a complete cross-resistance with zalcitabine (ddC) but only partial cross-resistance with zidovudine.

Pharmacokinetics and therapeutic use: Oral bioavailability of ddI is reduced by food and by chelating agents. The drug is eliminated by glomerular filtration and active tubular secretion, and the dose must be reduced in patients with renal dysfunction. Didanosine is used in HAART combination drug regimens.

Adverse effects: Pancreatitis is dose-limiting and occurs more frequently in alcoholic patients and those with hypertriglyceridemia. Other adverse effects include peripheral neuropathy, diarrhea, hepatic dysfunction, hyperuricemia, and the CNS effects.

Zalcitabine

Mechanisms of action: Zalcitabine is a pyrimidine nucleoside with mechanisms of action and resistance similar to those of other drugs. Depending on specific sites of

mutation on the *pol* gene, resistance may emerge to ddC alone or cross-resistance between other RT inhibitors may occur.

Pharmacokinetics and therapeutic use: Zalcitabine has high oral bioavailability. Dosage adjustment is needed in patients with renal insufficiency. Zalcitabine is always used in combination with other anti-HIV drugs.

Adverse effects: Dose-dependent peripheral neuropathy is the major adverse effect of ddC. Pancreatitis, esophageal ulceration, stomatitis, and arthralgias may also occur.

Lamivudine

Mechanisms of action: Like other drugs, lamivudine requires activation by host cell kinases and the drug is active against HIV-1, including strains resistant to zidovudine. Lamivudine is also effective in hepatitis B, and HBV nucleic acid is undetectable after treatment for 12 weeks.

Pharmacokinetics and therapeutic uses: Lamivudine is used orally in HAART regimens for the HIV and adjunctively with interferon alpha in HBV infection. Dosage adjustment is needed in patients with renal insufficiency.

Adverse effects of lamivudine are usually mild and include gastrointestinal distress, headache, insomnia, and fatigue.

Stavudine

Mechanisms of action: Stavudine is a thymidine analogue. Depending on specific sites of mutation on the reverse transcriptase gene, resistance may emerge to Stavudine alone, or cross-resistance between other NRTIs may occur.

Pharmacokinetics and therapeutic uses: Stavudine is used in HAART regimens. The drug has good oral bioavailability and penetrates most tissues, including the CNS. Dosage adjustment is needed in renal insufficiency.

Adverse effects: Peripheral neuropathy is dose-limiting.

Abacavir

Mechanisms of action: Abacavir is a guanosine analogue with mechanisms similar to those of other drugs.

Pharmacokinetics and therapeutic uses: There is good oral bioavailability, with metabolism via alcohol dehydrogenase and glucuronosyltransferase. Abacavir has been

used in combinations with zidovudinum and lamivudinum.

Adverse effects: Severe hypersensitivity reactions involving multiple organ systems may occur, occasionally with lethal outcome.

Inhypitors protease

Nelfinavir: This protease inhibitor is both an inducer and an inhibitor of hepatic cy-tochromes P450, so drag interactions are common. Its major adverse effect is a dose-limiting diarrhea.

Amprenavir: Amprenavir is a newer protease inhibitor which appears to be effective when used in combination with two NRTIs. It is an inhibitor of hepatic cytochromes P450. Skin rash occurs, in some cases leading to the Stevens-Johnson syndrome.

The use of protease inhibitors in HAART drug combinations has led to the development of disorders in carbohydrate and lipid metabolism. There are others such as sanquinavir, indinavir, ritonavir, neephinavir, atazanavir.

DRUGS FOR MALARIA TREATMENT

Chingaminum is a 4-aminoquinoline derivative. The drug is rapidly absorbed when given orally, is widely distributed to tissues, and has an extremely large volume of distribution. Antacids may decrease oral absorption of the drug. Chingaminum is excreted largely unchanged in the urine.

Mechanism of action: Chingaminum prevents polymerization of the hemoglobin break down product heme into hemozoin. Intracellular accumulation of heme is toxic to the parasite. Chingaminum is a weak base and may buffer intracellular pH, thereby inhibiting cellular invasion by parasitic organisms. The selective toxicity of the drug is due to an energy-dependent carrier mechanism in parasitized cells. Chingaminum-resistant parasites are able to expel the drug via a membrane P-glycoprotein pump.

Therapeutic uses: Chingaminum is the drug of choice for acute attacks of nonfalciparum and sensitive falciparum malaria and as a chemosuppressant, except in regions where *P falciparum* is resistant. The drug is solely a blood schizonticide and will not eradicate secondary tissue schizonts. Chingaminum has been used in

amebic liver disease in combination with metronidazolium and in autoimmune disorders including rheumatoid arthritis.

Adverse effects: At low doses, Chingaminum causes gastrointestinal irritation, skin rash, and headaches. High doses may cause severe skin lesions, peripheral neuropathies, myocardial depression, retinal damage, auditory impairment, and toxic psychosis. Chingaminum may also precipitate porphyria attacks.

Chinini sulfas is the principal alkaloid derived from the bark of the cinchona tree. Chinini sulfas is rapidly absorbed orally and is metabolized before renal excretion. Intravenous administration of chinini sulfas is possible in severe infections.

Mechanism of action: Chinini sulfas complexes with double-stranded DNA to prevent strand separation, resulting in block of DNA replication and transcription to RNA. Chinini sulfas is a blood schizonticide and has no effect on liver stages of the malaria parasite.

Therapeutic uses: The main use of chinini sulfas is in *P falciparum* infections resistant to Chingaminum. Chinini sulfas is sometimes used with doxycyclinum to shorten the duration of therapy and limit adverse effects. Quinidine, the dextrorotatory stereoisomer of chinini sulfas, is used intravenously in the USA for treatment of severe falciparum malaria. To delay emergence of resistance, the drugs should not be used routinely for prophylaxis.

Adverse effects: Chinini sulfas commonly causes **cinchonism**, whose symptoms include gastrointestinal distress, headache, vertigo, blurred vision, and tinnitus. Severe overdose results in disturbances in cardiac conduction which resemble quinidine adverse effects. Hematotoxic effects occur, including hemolysis in glucose-6-phosphate dehydrogenase-deficient patients. **Blackwater fever** (intravascular hemolysis) is a rare and sometimes fatal complication in chinini sulfas-sensitized persons. Chinini sulfas is an FDA Pregnancy Risk category X drug, contraindicated in pregnancy.

Melfloquinum is a synthetic 4-quinoline derivative chemically related to chinini sulfas. Because of local irritation, Melfloquinum can only be given orally,

though it is subject to variable absorption. Its mechanism of action is not known.

Therapeutic uses: The drug is recommended for prophylaxis in all malarious areas except those with no chingaminum resistance.

Adverse effects: Melfloquinum is less toxic than chinini sulfas; its adverse effects include gastrointestinal distress, skin rash, headache, and dizziness. At high doses melfloquinum may cause neurologic symptoms and seizures.

Primaquinum is a synthetic 8-aminoquinoline. Absorption is complete after oral administration and is followed by extensive metabolism.

Mechanism of action: Primaquinum forms quinoline-quinone metabolites, which are electron-transferring redox compounds which act as cellular oxidants. The drug is a tissue schizonticide and also limits malaria transmission by acting as a gametocide.

Therapeutic uses: Primaquinum is used to eradicate liver stages of *P vivax* and *P ovale* and should be used in conjunction with a blood schizonticide. Though not active alone in acute attacks of vivax and ovale malaria, a 14-day course of primaquinum is standard following initial treatment with chingaminum.

Adverse effects: Primaquinum is usually well tolerated but may cause gastrointestinal distress, pruritus, headaches, and methemoglobinemia. More serious adverse effects involves hemolysis in glucose-6-phosphate dehydrogenase-deficient patients.

Antifolate Drugs.

Classification and pharmacokinetics: The antifolate group includes chloridinum, proguanilum, sulfadoxinum, and dapsonum. All of these drugs are absorbed orally and are excreted in the urine, partly in unchanged form. Proguanil has a shorter half-life (12-16 hours) than other drugs in this subclass (half-life > 100 hours).

Mechanisms of action: Sulfonamides act as antimetabolites of the PABA and block folic acid synthesis in certain protozoans by inhibiting dihydropteroate synthase. Proguanilum (chloroguanide) is bioactivated to cycloguanil. Chloridinum and cycloguanilum are selective inhibitors of protozoan dihydrofolate reductases.

The combination of chloridinum with sulfadoxine has synergistic antimalarial effects through the **sequential blockade** of two steps in folic acid synthesis.

Therapeutic uses: The antifols are blood schizonticides which act mainly against *P. falciparum*. Chloridinum with sulfadoxine in fixed combination (Fansidar) is used in the treatment of Chingaminum-resistant forms of this species, although the onset of activity is slow. Many strains of *P. falciparum* are now resistant to antifols, and the drugs are not commonly used for prophylaxis because of their toxicities.

Adverse effects: The toxic effects of sulfonamides include skin rashes, gastrointestinal distress, hemolysis, kidney damage, and drug interactions caused by competition for plasma protein binding sites. Chloridinum may cause folic acid deficiency when used in high doses.

Antiamebial drugs

The agent of amebiasis is *Entamoeba histolytica*. It affects most commonly the small intestine (amebial dysentery). In this disease amebas are located in the lumen of the intestine and inside the intestinal wall. Amebas are able to spread along the system of portal vein and to cause the affection of the liver, lungs and other inner organs.

The antiamebial drugs are divided into 5 groups depending on their efficiency in various localization of the disease.

1) Drugs which are effective in any localization of the pathological process — nitroimidazolium derivatives (metronidazolium, tinidazolium, ornidazolium, secnidazolium, nirrtorazolium). They are highly-effective against amebas located inside the intestinal wall and in their extraintestinal localization. They are, however, only partially effective and not adequate as luminal amebicides (in such cases these drugs have to be combined with chiniofonum or iodoquinolum).

2) Luminal amebicides of direct action — a) 8-oxyquinoline derivatives (chiniofonum, iodoquinolum, clioquinolum); b) dichloracetamides (diloxanidi furoatum); c) antibiotics (paromomycinum, erythromycinum).

3) Luminal and intestinal wall amebicides of indirect action — tetracyclines (they inhibit the intestinal aerobic bacteria, which leads to the accumulation of oxygen and

promotes the eradication of amebas as they are anaerobes).

4) Tissue amebicides which are effective in the localization of amebas inside the intestinal wall and in the liver — emetines (emetine hydrochloride — it is introduced by the parenteral way, because in the peroral use it causes intense vomiting).

5) Tissue amebicides which are effective mainly in the localization of amebas in the liver — chloroquinum (chingaminum).

Emetinum is the alkaloid of ipecacuanha. It is also obtained by the synthetic way. The mechanism of its action is associated with the inhibition of protein synthesis. It is the high-toxic agent. The side effects are local irritating action (pain in the injection site), diarrhea, tachycardia, congestive heart failure.

Paromomycin is the antibiotic from the group of aminoglycosides. By its properties it is similar to streptomycinum, neomycinum, kanamycinum.

Drugs used for the treatment of giardiasis (lambliasis)

The agent of giardiasis is *Giardia lamblia (intestinalis)*. The main manifestations of the disease are duodenitis and enteritis. For the treatment of it such drugs as nitroimidazole derivatives (metronidazolium and others), aminoquinoline derivatives (aminoquinolum) and nitrofurans derivatives (furazolidonum) are used.

DRUGS FOR PNEUMOCYSTOSIS AND TOXOPLASMOSIS

Pentamidinum

Mechanism of action: Pentamidinum's mechanism of action is unknown but may involve inhibition of glycolysis or interference with nucleic acid metabolism of protozoans and fungi. Preferential accumulation of the drug by susceptible parasites may account for its selective adverse effects.

Therapeutic uses: Aerosol pentamidinum (once monthly) can be used in primary and secondary prophylaxis, though oral TMP-SMZ is usually preferred. Daily intravenous or intramuscular administration of the drug for 21 days is needed in the treatment of active pneumocystosis in the HIV-infected patient. Pentamidinum is also used in trypanosomiasis (see below).

Adverse effects: Severe adverse effects follow parenteral use including respiratory stimulation followed by depression, hypotension due to peripheral

vasodilation, hypoglycemia, anemia, neutropenia, hepatitis, and pancreatitis. Systemic adverse effects is minimal when pentamidine is used by inhalation.

Trimethoprim-Sulfamethoxazole is also used.

Antifols: Chloridine and Sulfonamides

Therapeutic uses: The combination of chloridine with sulfadiazine has synergistic activity against *Toxoplasma gondii* through the **sequential blockade** of two steps in folic acid synthesis.

Drugs used for the treatment of trichomoniasis

The agent of trichomoniasis is *Trichomonas vaginalis*. The main manifestations of this disease are vulvovaginitis in women and urethritis in men. In this disease the nitroimidazole derivatives (metronidazole, tinidazole, ornidazole, nitazoline), triazole derivatives (tenonitrozole), aminoquinoline derivatives (trichomonacidum), nitrofurazone derivatives (furazolidone and nifuratelum — locally) are used.

DRUGS FOR TRYPANOSOMIASIS

Pentamidine is commonly used in the hemolympathic stages of disease caused by *Trypanosoma gambiense* and *T rhodesiense*. Because it does not cross the blood-brain barrier, pentamidine is not used in later stages of trypanosomiasis. Other therapeutic uses include pneumocystosis and treatment of the kala azar form of leishmaniasis.

Melarsoprolum: This drug is an organic arsenical which inhibits enzyme sulfhydryl groups. Because it enters the CNS, melarsoprolum is the drug of choice in African sleeping sickness. Melarsoprolum is given parenterally because it causes gastrointestinal irritation; it may also cause a reactive encephalopathy which can be fatal.

Nifurtimox: This drug is a nitrofurazone derivative which inhibits the parasite-unique enzyme trypanothione reductase. Nifurtimox is the drug of choice in American trypanosomiasis and has also been effective in mucocutaneous leishmaniasis. The drug causes severe adverse effects, including allergies, gastrointestinal irritation, and CNS effects.

Suraminum: This polyanionic compound is a drug of choice for the early

hemolymphatic stages of African trypanosomiasis (before the CNS involvement). It is also an alternative to ivermectin in the treatment of onchocerciasis. Suramin is used parenterally and causes skin rashes, gastrointestinal distress, and neurologic complications.

DRUGS FOR LEISHMANIASIS

Leishmania, parasitic protozoa transmitted by flesh-eating flies, cause various diseases ranging from cutaneous or mucocutaneous lesions to splenic and hepatic enlargement with fever. **Solusurminum** (pentavalent antimony), the primary drug in all forms of the disease, appears to kill the parasite by inhibition of glycolysis or effects on nucleic acid metabolism, antimony blocks SH groups. Adverse effects: asthenia, headache, anemia, hepatitis. Alternative agents include pentamidine (for visceral leishmaniasis), metronidazole (for cutaneous lesions), and amphotericin B (for mucocutaneous leishmaniasis).

AGENTS USED FOR TREATMENT OF LEPROSY

Sulfones

The sulfones, the principal class of agents used to treat leprosy, are chemically related to the sulfonamides. The most important derivatives come from **dapsone**.

Mechanism of action: Dapsone is bacteriostatic for *Mycobacterium leprae*. Its mechanism of action is similar to that of the sulfonamides.

Pharmacokinetics: Dapsone is slowly but completely absorbed from the gastrointestinal tract. b. It undergoes intestinal reabsorption from the bile, resulting in a sustained level of the drug in the circulation. c. It is principally excreted in the urine.

Pharmacologic effects: Dapsone is effective against *M. leprae*, although resistance to the drug can develop. It is bacteriostatic for *M. tuberculosis* in vitro.

Therapeutic uses: Dapsone is the most important drug in the treatment of leprosy. Because of recent resistance to dapsone, it is now usually given with rifampicin, or with clofazimine, or with both.

Adverse effects: The most common untoward effects include hemolysis, methemoglobinemia, nausea, vomiting, rash, transient headache, and anorexia. The

sulfones can cause an exacerbation of lepromatous leprosy. A fatal infectious mononucleosis-like syndrome has been reported.

ANTIHELMINTICS

These drugs are used to treat parasitic infections due to flatworms and roundworms. Anthelmintic drugs have diverse chemical structures, mechanisms of action, and properties. Many of them act against specific parasites, and few are devoid of significant toxicity to host cells. In addition to the direct toxicity of the drugs, reactions to dead and dying parasites may cause serious toxicity in patients. In the text that follows, the drugs are divided into three groups on the basis of the type of helminth primarily affected (nematodes, trematodes, and cestodes).

Drugs which act against nematodes

The medically important intestinal nematodes responsive to drug therapy include *Enterobius vermicularis* (pinworm), *Trichuris trichiuria* (whipworm), *Ascaris lumbricoides* (roundworm), ancylostoma and necator species (hookworms), and *Strongyloides stercoralis* (threadworm). Over one billion persons worldwide are estimated to be infected by intestinal nematodes. Tissue nematodes responsive to drug therapy include ancylostoma species, which cause cutaneous larva migrans, seen primarily in the southern USA. Species of dracunculus, onchocerca, toxocara, and *Wuchereria bancrofti* (the cause of filariasis) are all responsive to drug treatment. The number of persons worldwide estimated to be infected by tissue nematodes exceeds 0.5 billion.

Diethylcarbamazine is the drug of choice for filaria worms. It effectively treats *Wuchereria bancrofti*, *Wuchereria malayi*, *Loa loa*, and *Onchocerca volvulus*. Diethylcarbamazine immobilizes microfilariae by an unknown mechanism, increasing their susceptibility to host defense mechanisms. Diethylcarbamazine is the drug of choice for filariasis and an alternative drug, when used in combination with suramin, for onchocerciasis. Microfilariae are killed more readily than adult worms. The drug is rapidly absorbed from the gut and is excreted in the urine.

Adverse effects include headache, malaise, weakness, and anorexia. Reactions to proteins released by dying filariae include fever, rashes, ocular damage,

joint and muscle pain, and lymphangitis.

Praziquantelum is a broad-spectrum anthelmintic that is considered one of the drugs of choice for tapeworm infections and the drug of choice for the treatment of schistosomiasis and other fluke infections.

Mechanism of action: Praziquantelum increases membrane permeability to calcium, causing marked contraction initially and then paralysis of trematode muscles; this is followed by vacuolization and parasite death.

Therapeutic uses: Praziquantelum has a wide anthelmintic spectrum which includes activity in both trematode and cestode infections. It is the drug of choice in schistosomiasis (all species), clonorchiasis, and paragonimiasis and for infections caused by small and large intestinal flukes. The drug is active against immature and adult schistosomal forms. Praziquantelum is also one of two drugs of choice (with niclosamidum) for infections due to cestodes (all common tapeworms) and in the treatment of cysticercosis.

Pharmacokinetics: Absorption from the gut is rapid, and the drug is metabolized by the liver to inactive products.

Adverse effects include headache, dizziness, malaise, and, less frequently, gastrointestinal irritation, skin rash, and fever. Praziquantelum is contraindicated in ocular cysticercosis.

Drugs of wide actions

Mebendazolum acts by selectively inhibiting microtubule and ATP synthesis and glucose uptake in nematodes.

Therapeutic uses: Mebendazolum is a drug of choice for pinworm and whipworm infections. It is one of two drugs of choice (with pyranteliy parmoatum) for roundworm and for combined infections with ascarids and hookworm. Mebendazolum can also be used as a backup drug in certain cestode and trematode infections. Less than 10% of drug is absorbed systemically after oral use, and this portion is metabolized rapidly.

Adverse effects: Mebendazolum toxicity is limited to gastrointestinal irritation. The drug is contraindicated in pregnancy because of possible embryotoxicity. It may

cause fever, headache, vomiting, and neutropenia.

Albendazole blocks glucose uptake in both larval and adult parasites, which leads to decreased formation of ATP and subsequent parasite immobilization. The actions of albendazole may also include inhibition of microtubule assembly, as has been described for mebendazole and thiabendazole.

Therapeutic uses: Albendazole has a wide anthelmintic spectrum. It is an alternative drug for larva migrants, for ascariasis, and for infections caused by roundworms, whipworms, hookworms, pinworms, and threadworms. Albendazole is also active against the pork tapeworm in the larval stage. **Adverse effects:** Albendazole has few toxic effects during short courses of therapy. Reversible leucopenia, alopecia, and changes in liver enzymes may occur with prolonged use. Long-term animal toxicity studies report bone marrow suppression and fetal toxicity.

Chemotherapy of cestodes

Niclosamide (Phenacemide) is one of the drugs of choice for the treatment of most tapeworms, including *Diphyllobothrium latum*, *Taenia saginata*, and *Hymenolepis nana*. Niclosamide may act by uncoupling oxidative phosphorylation or by activating ATPases.

Therapeutic uses: Niclosamide is one of two drugs of choice (with praziquantel) for infections caused by beef, pork, and fish tapeworm infections. However, it is not effective in cysticercosis (for which albendazole or praziquantel is used) or hydatid disease caused by *Echinococcus granulosus* (for which albendazole is used). Scoleces and cestode segments are killed, but ova are not. Niclosamide is effective in the treatment of infections due to small and large intestinal flukes.

Adverse effects are usually mild but include gastrointestinal distress, headache, rash, and fever. Some of these effects may result from systemic absorption of antigens from disintegrating parasites.

Extractum Filicis maris spissum causes paralysis of helminth muscle. Therapeutic use: hymenolepidosis, teniasis. Adverse effects: nausea, vomiting, headache.

Chloxylum causes destruction of nucleoproteins in cells of intestinal epithelium and parenchyma of trematodes in liver, oppresses carbohydrate metabolism, paralyzes musculature of helminthes.

Therapeutic uses: Hepatic helminthiasis, opisthorchiasis, fascioliasis. **Adverse effects:** Dizziness, somnolence, pains in liver area, allergic reactions.

Stibii et Natrii tartars cause oppression of enzymatic systems in helminthes.

Therapeutic uses: opisthorchiasis, schistosomiasis.

Adverse effects: nausea, vomiting, arthralgia, skin rashes, and fever.

Chemotherapy of nematodes

Pyranteli palmoas is one of the drugs of choice for the treatment of ascariasis, hookworm, and pinworm. It produces persistent nicotinic activation, resulting in spastic paralysis of the worms. Pyranteli palmoas and its congener, **oxanteli palmoas**, stimulate nicotinic receptors present at neuromuscular junctions of nematodes. Contraction of muscles occurs, followed by a depolarization-induced paralysis.

Therapeutic uses: Pyranteli palmoas is one of two drugs of choice (with mebendazole) for infections due to hookworm, pinworm, and roundworm. The drug is poorly absorbed when given orally.

Adverse effects are minor but include gastrointestinal distress, headache, and weakness.

Piperazini adipinas is an alternative drug for the treatment of ascariasis and pinworms. This agent is thought to block the response of *Ascaris* muscle cells to acetylcholine; the flaccid worm can then be expelled by peristalsis. Piperazini adipinas paralyzes ascaris by acting as an agonist at the GABA receptors. The paralyzed roundworms are expelled live by normal peristalsis.

Therapeutic uses: Piperazini adipinas is an alternative drug for ascariasis. Mild gastrointestinal irritation is the most common **side effect**. Piperazini adipinas should not be used in patients with seizure disorders.

Thiabendazolum is very effective against cutaneous and visceral larva migrans and strongyloidiasis. It is also used in trichinosis. Thiabendazolum is a

structural congener of mebendazole and has a similar action on microtubules.

Therapeutic uses: Thiabendazolum is a drug of choice for visceral forms of larva migrans and is an effective drug for treatment of strongyloidiasis, cutaneous larva migrans, and threadworm infections. Thiabendazolum is rapidly absorbed from the gut and is metabolized by liver enzymes. The drug has anti-inflammatory and immunorestorative actions in the host.

Adverse effects include gastrointestinal irritation, headache, dizziness, drowsiness, leukopenia, hematuria, and allergic reactions, including intrahepatic cholestasis. Reactions caused by dying parasites include fever, chills, lymphadenopathy, and skin rash.

Ivermectin, although still an investigational drug, has become the drug of choice for onchocerciasis (river blindness). Ivermectin intensifies GABA-mediated neurotransmission in nematodes and causes immobilization of parasites, facilitating their removal by the reticuloendothelial system. Selective toxicity results because in humans GABA is a neurotransmitter only in the CNS, and ivermectin does not cross the blood-brain barrier.

Therapeutic use: Ivermectin is the drug of choice for onchocerciasis, acts more slowly than diethylcarbamazine, and causes fewer systemic and ocular reactions. Ivermectin is also the drug of first choice for strongyloidiasis and an alternative agent in filariasis. Single-dose oral treatment in onchocerciasis results in Mazzotti reactions which include fever, headache, dizziness, rashes, pruritus, tachycardia, hypotension, and pain in joints, muscles, and lymph glands. These symptoms are usually of short duration, and most can be controlled with antihistamines and nonsteroidal anti-inflammatory drugs.

Levamisolum inhibits succinic dehydrogenase, thus oppressing reaction of reduction of fumaric acid and disturbs bioenergetics process in helminthes. Increases immunity.

Therapeutic use: Ascariasis, strongyloidiasis, hookworm disease (ancylostomiasis); to increase immunity in chronic rheumatoid arthritis and glomerulonephritis.

Adverse effects. Headache, insomnia, dyspepsia, altered olfaction, allergic reactions.

Naphthammonum. Causes contracture of parasites' musculature, thus promote their removal from intestine.

Therapeutic use: Enterobiasis, trichocephaliasis, ascariasis, strongyloidosis, ancylostomiasis.

Adverse effects. Nausea, abdominal pains. In overdosage – muscle weakness, tremor, and neurotoxicosis.

№	Drug	Drug forms
1.	Mebendazolum	Tab. 0,1
2.	Levamisolum	Tab. 0,05, 0,15
3.	Pyrantelum	Tab. 0,25, 0,125; Susp. 5% - 15ml
4.	Prasiquantelum (Biltricid)	Tab. 0,6
5.	Piperazini Adipinas	Tab. 0,5, 0,2; 5% - 100ml
6.	Naphthammonum	Tab. 0,5
7.	Phenasalum	Pulv.
8.	Stibio-Natrium Tartaricum	Pulv.
9.	Extr. Filicis Maris Spissum	Caps. 0,5
10.	Chloxylum	Pulv.

Vitamins drugs

Vitamins drugs are medicaments which by chemical structure similar vitamins, their analogues, their predecessors. They are used for substitution of vitamins for treatment hypo- and avitaminoses; adaptation – stimulation of metabolic reaction of organism; pharmacodynamic action which means therapeutic use of vitamins in treatment of different diseases. Russian scientist N.I. Lunin (1880) paid attention on

the fact that besides proteins, lipids, carbohydrates food consists of other substances. Holland Christian Echman had supposed that rice husk contained substance for prevention and treatment of disease bery-bery (1897). In 1911 a Polish K. Funck separated from rice husk a component which was called vitamin.

Vitamins drugs are classified into:

1. Water-soluble vitamins drugs.

2. Fat-soluble vitamins drugs.

Water-soluble vitamins are the B₁, C, P.

Thiamini chloridum – vitamine drug of B₁

Pharmacokinetics: Thiamini chloridum is absorbed in intestines quickly. In organism it is phosphorylated in mitochondries, microsomes and gialoplasms of cells. Thiamini chloridum is excreted with urine.

Pharmacodynamics: There are three main effects of Thiamini chloridum. Cardiotrophic action. Thiamini chloridum widens coronar vessels by means of adenosine, in creates oxygenation of myocardium, improves trophic and contractility of myocardium, decreases acidosis. Neurotrophic action. Thiamini chloridum promotes accumulation of acetylcholine, improves impulses conduction in nervous fibres. There are receptors to thiamines. Thiamini chloridum interracts with receptors and modulate ions currents, decreases nonoxidative products quantity and has analgetic effect. 3. Hypoglycemic action. Thiamini chloridum improves utilization of glucose, is sinergist of insuline.

Mechanism of action: Thiamini chloridum after phosphorylation is a part of coenzymes of dehydrogenase which take part in oxidation of Ketoacids glucose' utilization, removes acidosis. Thiamini chloridum (B₁) is coenzyme of transketolaze, which takes part in pentosophosphate way of glucose metabolism. Thiamini chloridum activates NAD, acetylcholine, nucleinic acids, AMP, adenosine' synthesis and other processes.

Therapeutic use: Hypo- and avitaminoses, neuritis, polyneuritis, radiculitis, diabetes mellitus, ischaemia, heart diseases, chronic heart failure, gaster and duodenum ulcers, skin diseases.

Adverse effects: allergic reactions, itch, anaphylactic shock; nausea; hypotension, collapse, inhibition of the CNS and breathing, ataxia, lethargy; high doses inhibit activity of liver enzymes; riboflavinum decreases cardiac glycosides toxicity.

Riboflavinum (B₂)

Pharmacokinetics: Riboflavinum is absorbed into intestines, phosphorylated in mucosa of intestines in liver and blood. Riboflavinum is accumulated in liver, kidneys, adrenals, excreted by kidneys. Urine is coloured in light yellow colour.

Pharmacodynamics: Riboflavinum increases organism stability to oxygen deficiency (hypoxia). Riboflavinum intensifies growth and regeneration of tissues. Riboflavinum improves function of vision. Riboflavinum activates hemoglobin synthesis.

Mechanism of action: after phosphorylation Riboflavinum becomes a component of FAD, FMN coenzymes (flavoproteins), involved in many oxidative reduction reactions.

Therapeutic use: Hypo- and avitaminoses; eye atrophy process (keratitis, conjunctivitis, iritis); skin diseases; infectious diseases; radiation sickness, leukemia, anemia; asthenia.

Adverse effects: the irritative influence on kidneys' parenchyma.

Acidum nicotinicum (B₃, PP)

Pharmacokinetics: Acidum nicotinicum is absorbed intensively in stomach, biotransformed in liver, **excreted with urine and metabolites.**

Pharmacodynamics: Acidum nicotinicum has sedative and antiepileptic influence on the CNS, neuroprotective effect, interacts with benzodiazepine receptors. Acidum nicotinicum has cardiotropic and light cardiotonic action. Acidum nicotinicum dilates the vessels, decreases blood pressure. Acidum nicotinicum improves metabolism, functioning processes of liver, has glycogenolytic function. Acidum nicotinicum activates fibrinolysis and has antiaggregant action. Acidum nicotinicum decreases cholesterol and fatty acid concentration, tryglyceride synthesis in blood, decreases formation and secretion of

very low density lipoproteins by the liver. This action appears secondary to its ability to inhibit fatty acid mobilization from adipose tissue. Since very low density lipoproteins is the source of low density lipids acidum nicotinicum lowers low density lipoproteins. Acidum nicotinicum has hypoglycemic action. Acidum nicotinicum stimulates stomach and intestines activity. Acidum nicotinicum increases productions of thyroxine and glucocorticoids

Mechanism of action: Acidum nicotinicum is transformed into nicotinamide which is a coenzyme NAD and its phosphate NADP involved in oxydative-reduction reactions, acts as hydrogen acceptor and takes part in the electron transport chain in tissue respiration.

Therapeutic use: Pellagra, liver impairment, atherosclerosis, spasms of peripheral vessels, ischemic diseases of heart, gastritis, gastric ulcers, radiation sickness.

Adverse effects: skin hyperemia, loss of appetite, itches, nausea, vomiting, hypotension, collapse, dizziness, congestion, in high doses – lipid liver infiltration.

Calcii pantothenas (B₅)

Pharmacokinetics: Calcii pantothenas is absorbed well, distributed evenly, excreted with urine.

Pharmacodynamics: Calcii pantothenas has neurotrophic effect, improves neurotransmission. Calcii pantothenas improves skin trophy and respiration. Calcii pantothenas regulates activity of intestines.

Mechanism of action: Calcii pantothenas takes part in formation of coenzyme A and acyl carrier protein and in synthesis of corticosteroids, mediators ATP, methabolism of fatty acids, citric acids, absorption of vitamin E, Kalium, transport of acyl units.

Therapeutic use: Neuritis, neuralgia, allergy, respiratory system and skin diseases, burn ulcers, intestinal atony.

Adverse effects: dyspepsia.

Pyridoxini hydrochloridum (B₆)

Pharmacokinetics: Pyridoxini hydrochloridum is absorbed in connective

status. It is liberated from that status under influence of digestive juices and absorbed again. Pyridoxini hydrochloridum may be in three forms: pyridoxini hydrochloridum, pyridoxaminum, pyridoxalum. It is phosphorylated in tissues. 90% of Pyridoxini hydrochloridum is oxydated and excreted with urine.

Pharmacodynamics: Pyridoxini hydrochloridum has positive inotropic and negative chronotropic action more in the congestive heart failure. It improves myocardial trophic reactions. Pyridoxini hydrochloridum activates secretion of bile, formation of glycogen, proteins, it has desintoxication function. Pyridoxini hydrochloridum improves synaptic neurotransmission, the CNS trophy, peripheral nerve system functioning. Pyridoxini hydrochloridum stimulates hemopoiesis, more leukopoesis. Pyridoxini hydrochloridum normalises: lipid metabolism, decreases cholesteryne level.

Mechanism of action: Pyridoxini hydrochloridum is phosphorylated in liver, forms of transaminases and decarboxylases coenzymes, activates amino acids absorption, their desamination, periamination, decarboxylation, formation of dopamine, histamine- and amino-levolenic acid. It takes part in metabolism of serotonin, the GABA, acidum glutaminicum, promotes transition of linoleic acid into arachidonic acid.

Therapeutic use: Neuritis, radiculitis, chorea, Parkinsonism, epilepsy, liver impairment, hypo- and avitaminoses, chronic cardiac failure, myocardiodystrophy, aplastic anemia, radiation sickness, gestational toxicosis, alcoholism treatment with anti-TB drugs.

Adverse effects: Allergy, reduce prolactin secretion, damage sensor nerves and liver.

Cyanocobalaminum (B₁₂)

Pharmacokinetics: In stomach cyanocobalaminum connects with gastromucoprotein (intrinsic factor) and is absorbed in intestines (ileum). In blood cyanocobalaminum connects (till 93%) with globuline, from blood it entrances into liver, transforms into active form – cobamamidum. 50% of cyanocobalaminum is excreted with urine, 6-7% with faecies.

Pharmacodynamics. Cyanocobalaminum stimulates hemopoiesis. Cyanocobalaminum regulates epithelium forming. Cyanocobalaminum regulates nerve system functioning and formation of myeline. Cyanocobalaminum stimulates regeneration processes and growth. Cyanocobalaminum stimulates fat formation and utilization. Cyanocobalaminum deficiency results in pernicious anemia which is characterized by megaloblastic anemia and neuropathies. Absorption of cyanocobalaminum from the gastrointestinal tract requires the presence of gastric intrinsic factor lack of those results in pernicious anemia.

Mechanism of action: after transmission to cobalamide: it takes part as coenzyme of acidum folicum reductase in purine and pyrimidine synthesis, nucleonic acid metabolism, erythrocytes formation. After converting to deoxyadenosyl cobalamine and methylcobalamine it is essential for the conversion of homocysteine to methionine. Cyanocobalaminum takes part in cell growth and multiplication, synthesis of myeline, thiol compounds: glutathione, methionine, choline, nucleinic acids; has immunotrophic, regenerative activity.

Therapeutic use: Megaloblastic anemia, macrocytic anemia, hypovitaminosis, pernicious anemia, neuritis, neuralgia, radiculitis, radiation sickness, leucemia, infection diseases, diseases of liver, dystrophia of children.

Adverse effects: excitation, tachycardia, cardiac pains, and allergy.

Acidum folicum (B₉)

Pharmacokinetics: After oral administration drug quickly and fully is absorbed mainly in intestines. It transports from blood to liver, deponates, 50% is excreted with urine, other with feces.

Pharmacodynamics: Acidum folicum takes part in many biosynthetic and other metabolic reactions, provides for normoblastic hemopoiesis including erythropoiesis, leucopoiesis, trombocytogenesis, stimulates immune system, regeneration.

Mechanism of action: Its active form is folinic acid (tetrahydrofolate) which take in carrier of activated one carbone units, synthesis of purines, pyrimidines compounds, nucleonic acids. Those are taking part in synthesis of histidine, choline, methionine, purine and pyrimidines, nucleinic acid synthesis of erythrocytes,

trombocytes, leucocytes.

Therapeutic use: different anemias in children, pregnant, radiation sickness, spru (macrocytic, megaloblastic anemias), pregnancy, lactation.

Adverse effects: Allergy, damage of kidney epithelium.

Calcii pangamas (B₁₅)

Pharmacokinetics: Calcii pangamas is absorbed fully, distributed evenly, excreted with urine.

Pharmacodynamics: Calcii pangamas has cardioprotective effect because activates synthesis of creatine and creatine phosphate. Calcii pangamas has neuroprotective effect because activates of choline and acetylcholine. Calcii pangamas has antidystrophic effect because activates synthesis of creatinephosphate and glycogen in muscle, utilization of oxygen by tissues and protect hypoxia. Calcii pangamas has hepatoprotective effect because stimulates formation of choline phosphatidilcholine and glycogen in liver.

Mechanism of action: Acidum pangamicum is donator of methylgroups and forms choline, creatine.

Therapeutic use: Liver diseases, dystrophic damages of myocardium, ischemic heart diseases, atherosclerosis, alcoholism.

Adverse effects: Abdominal pain, allergy.

Acidum ascorbinicum (C)

Pharmacocinetics: Acidum ascorbinicum is absorbed in intestines distributed in all tissues and organs. In organism under influence the substances with P-vitamine activity (vitaminum P, catechines, gallic acids) transforms into dehydroascorbic acid which has vitamin properties. It excreted with urine. Alcohol and smoking accelerate transformation of acidum ascorbinicum into nonactive metabolite.

Pharmacodynamics: Acidum ascorbinicum activates synthesis of collagen and procollagen, providing of bones' grows and formation of cartilages and dentine. Acidum ascorbinicum transforms acidum folicum into acidum tetrahydrofolicum which promotes proteins and nucleinic acids synthesis. Acidum ascorbinicum improves function of sympathetic nervous system, activates catecholamines'

synthesis. Acidum ascorbinicum stimulates erythropoiesis, improves absorption of iron. Acidum ascorbinicum activates nonspecific protective function of organism (increases interferone' synthesis, antibodies' formation, intensifies fagocytosis, migration and hemotaxis of leucocytes. Acidum ascorbinicum promotes corticosteroids synthesis. Acidum ascorbinicum intensifies cholesterine metabolism. Acidum ascorbinicum intensifies desintixycate of xenobiotics and synthesis in liver. Acidum ascorbinicum inhibits peroxides and cancerogenic substances formation, it increases organism stability to oxygen deficiency, so it is antioxydant. In high doses acidum ascorbinicum hinders insuline release. Acidum ascorbinicum decreases vessels permeability.

Mechanism of action: Acidum ascorbinicum is donator and acceptor of hydrogen groups, its role is related to its ability to act as an oxidation-reduction system.

Therapeutic use: Hypovitaminosis, infections diseases, hemorrhagic diatheses, bleeding, intoxication, atherosclerosis, heart, hepatic, renal impairment, radiation, sickness, diseases of respiratory ways, for stimulation of protective powers of organism.

Adverse effects: In high doses acidum ascorbinicum inhibits β cells of Langerhans's islands, forms of kidney concrements, promotes hypertension, increases of coagulation, results in diarrhea due to intestinal irritation.

Rutinum (vitaminum P)

Pharmacokinetics: Rutinum is absorbed fully, distributed in all tissues and organs, and is more excreted with urine.

Pharmacodynamics: Rutinum promotes capillary permeability and increases stability of organism to oxygen deficiency.

Mechanism of action: Rutinum has antioxydant action, prevents acidum ascorbinicum, catecholamines oxydation, lengthens its action, and decreases gialuronidase activity, promotes transformation of acidum ascorbinicum into acidum dehydroascorbinicum and its accomodation.

Therapeutic use: Hypovitaminosis, leukemia, bleeding, hemorrhagic diathesis,

capillary toxicosis, prominent disease.

Adverse effects: Allergy.

Quercetinum is also a drug of vitaminum P, it has more cardioprotective activity, decreases ulcerogenic effects of nonsteroid antiinflammatory drugs, is used in capillary fragility also. There are complex drugs which consist of acidum ascorbinicum and Rutinum – **Galascorbinum** and **ascorutinum**.

Fat – soluble vitamins

Retinoli acetat (A)

Pharmacokinetics: Retinolum is absorbed quickly in intestines. In the presence of bile acids it emulgates, forms micells which contain bile acids, cholesterine, fatty acids. It is necessary to include fat in food. Retinolum is accumulated in liver. It may be transformed and existed in three forms: retinolum, retinalum, acidum retinoicum which are excreting predominantly excreted with urine.

Pharmacodynamics: Retinolum stimulates regenerative processes, prevents damages of epithelium cells, normalizes structure of epithelium cells. Retinolum promotes growth of organism, prevents bones' epiphyses calcification. Retinolum provides normal visual purple (for night vision). Retinolum activates immunogenesis. Retinolum supports reproductive function. Retinolum improves trophy of myocardium, skeletal muscles, liver, and nervous system. Retinolum has antioxydant and antisclerotic action. Retinolum normalizes reologic properties of blood.

Mechanism of action: Retinolum stimulates oxydative reduction processes in cells, intensifies their proliferation and differentiation. Retinolum promotes synthesis of visual purple – rhodopsin. Retinolum activates release of somatotropic hormone, thyreoid etc. Retinolum activates synthesis of immunoglobulines, antibodies, lisosome enzymes. Retinolum activates glycogen deposite in muscles, heart and liver. Retinolum regulates metabolism of phospholipides synthesis of nucleonic acids, proteins, enzymes.

Therapeutic use: Hypo- and avitaminosis, skin diseases, cornea and retina diseases, burns, frostbites, rachitis, infectious, liver diseases, bronchopulmonary diseases, gastric, intestines diseases, in complex therapy of rachitis, in stomatology.

Adverse effects: Fatigue, head ache, sleepiness, nausea, vomiting, photophobia, convulsions, rashes, skin pigmentation, bone pains, liver and spleen enlargement, other symptoms of hypervitaminosis.

Beta-carotenes are prodrugs of retinolum, have antiradiative immunomodulatory action.

Ergocalciferolum (D₂) and **Cholecalciferolum (D₃)** are biological active formes of vitamin D.

Pharmacokinetics: As other fat-soluble vitamins Ergocalciferolum is absorbed by means of bile acids, transports into lymph caniculas, and to the liver. In plasma of blood it transports in connective status by means of calciferol connective protein transcalferrine. It deposits in bones, liver, mucosa of intesties. In liver it is transformed into calcidiolum, in kidney – into calcitriolum. It is excreted with bile, and then it is absorbed again and excreted with urine and feces.

Pharmacodynamics: Ergocalciferolum in form of calcitriolum promotes synthesis of proteins (phosphatase and other) which intensifies absorption of calcium in intestines and kidney and synthesis of proteins which connect calcium in bones and tissue. It increases calcium and phosphorus concentration in blood and regulates bone mineralization, it stimulates immune system and regeneration.

Mechanism of action: Ergocalciferolum regulates calcium and phosphorus metabolism, its absorption and mobilization from bone.

Therapeutic use: Hypovitaminosis, rachitis prophylaxis and treatment, bone fractures, skin diseases, osteoporosis, osteomalacia.

Adverse effects: bone demineralization, calcium transport and deposit in vessels, kidneys, liver, heart, intestines (calcinosis), the CNS damage, lever, sickness, sleeping, diseases of appetite, pain in stomach, dyspepsia, increase of arterial pressure, heart insufficiency.

Treatment of D hypervitaminosis: administration of antioxydants (vitamin E, C, A), drugs which intensifies biotransformation of vitamin D (phenobarbitalum) and remove acidosis (natrii hydrocarbonas), drugs which contain Kalium and magnesium, glucocorticoides and drugs which prevent demineralization of bones

(calcitrium) oleum jecoris Aselli has properties of vitamins A and D. Videinum and cholecalciferolum are drugs of vitamins D₃.

Tocopheroli acetas (E)

Pharmacokinetics: Tocopheroli acetas is absorbed mainly in proximal part of ileum by means of bile acids. It transports to lymph and blood and then to all tissues of organism, includes into lipoprotein, membranes of mitochondrias and microsomes. The most concentration of Tocoferoli acetas is in adrenals and fatty tissues. It is excreted in nontransformed status with feces.

Pharmacodynamics: Tocopheroli acetas normalizes protein and fat metabolism. Tocopheroli acetas has membrane protective action. Tocopheroli acetas regulates reproductive action. Tocopheroli acetas activates erythropoiesis and improves rheological properties of blood. Tocopheroli acetas prevents atherosclerotic damage of vessels. Tocopheroli acetas has tocolytic action. Tocopheroli acetas has cardioprotective action (improves oxygenation and enzymes activity of myocardium, prevents the development of dystrophic processes in myocardium, in skin, normalizes permeability of vessel walls, takes part in regeneration processes, in absorption of iron.

Mechanism of action: Tocoferoli acetas is antioxydant. Tocoferoli acetas increases activity of creatinphosphokinase, Na⁺K⁺-ATPase, cytochrome-C-oxydase, stimulates synthesis of ubichinonum, improves tissues respiration. Tocoferoli acetas promotes formation of hem, increases synthesis of nucleotides, hormones (gonadotropines of hypophysis and placenta) and enzymes. Tocoferoli acetas decreases thrombocytes aggregation. Tocoferoli acetas promotes surphactants synthesis. Tocoferoli acetas promotes formation of follicles, development of spermatozoids. Tocoferoli acetas improves iron absorption.

Therapeutic use: hypovitaminosis, heart, skin, hepatic, gerontologic diseases, sexual glands function impairment, atherosclerosis, prophylaxis, spontaneous abortions, myodistrophy, angina, climax, peripheral vessels impairment, rheumatoid arthritis, stress and radiation, thrombophlebitis, endarteritis, complex therapy of anemias, paradonthosis, for treatment of hypervitaminosis D.

Adverse effects: disturbances of liver function, allergy, nausea, headache.

Vicasolum (water soluble drug of vitamin K)

Pharmacokinetics: Vicasolum is absorbed quickly and fully excreted with urine and feces.

Pharmacodynamics: Vicasolum increases blood coagulation, formation of thrombus.

Mechanism of action: Vicasolum stimulates synthesis of prothrombin, proconvertine and IX, X factors of coagulation in liver. Vicasolum forms of ATP, creatinephosphate and activates enzymes.

Therapeutic use: hemorrhages, hepatitis, liver cirrhosis, chronic diarrheas, ulcers, metrorrhagias, preparation to operation.

Adverse effects: hemolytic anemia, liver damage, increases of thrombus formation.

Polyvitamine drugs

There are many polyvitamins drugs without mineral, for example Decamevitum, “Glutamevitum” and with mineral Quadevitum, Vitamum etc. Polyvitamines drugs – complexes of vitamins in balance correlation for intensification of its effect, they activate different biochemical processes in organism and stimulate function of organs.

Antivitamins

There are different groups of antivitamins. The first group consists of antimetabolites which are chemical analogues of vitamins, for example neodicumarinum is antivitamin of Vicasolum, isoniazidum of pyridoxini hydrochloridum and acidum nicotinicum. The second group includes specific inactivators of vitamins, for example thiaminasa.

№	Drug	Drug forms
1.	Thiamini chloridum	Tab. 0,002, 0,005; Amp. 2,5%, 5% - 1ml

2.	Riboflavinum	Tab. 0,002, 0,005, 0,01, Guttas 0,01% - 10ml
3.	Pyridoxini hydrochloridum	Pulv.; Tab. 0,002, 0,005, 0,01; Amp. 1%, 5% - 1ml
4.	Acidum Nicotinicum	Pulv.; Tab. 0,05; Amp. 1% - 1ml
5.	Nicotinamidum	Pulv.; Tab. 0,005, 0,015, 0,025; Amp. 1%, 2,5% - 1ml
6.	Cyanocobalaminum	Amp. 0,003%, 0,01%, 0,02%, 0,05% - 1ml
7.	Acidum Folicum	Pulv.; Tab. 0,001
8.	Acidum Ascorbinicum	Pulv.; Tab. 0,05, 0,1; Dragee 0,05; Amp. 5%,10% - 1ml
9.	Rutinum	Pulv.; Tab. 0,02
10.	Calcii Pantothenas	Pulv.; Tab. 0,1; Amp. 20% - 2ml
11.	Calcii Pangamas	Tab. 0,05
12.	“Ascorutinum”	№ 50

	Drug	Drug forms
	Retinoli Acetas	Tab. 33000 IU (0,0135); Dragee 3300 IU (0,001);

		Flac. sol. ol. 3,44% (1ml – 100000 IU), 6,88% (1ml – 200000 ME), 8,6% (1ml – 250000 IU) – 10ml; Caps. 0,86% (5000 IU), 5,68% (33000 IU) – 0,2ml sol. ol.
	Ergocalciferolum	Dragee 500 IU; Sol. ol. 0,0625% (1ml – 25000 U), 0,125% (1ml – 50000 IU); sol. spirit. 0,5% (1ml – 200000 IU) – 10ml
	Tocopheroli Acetas	Caps. 50% - 0,1, 0,2ml; Sol. oleosa 5%, 10%, 30% - 10, 20, 25, 50ml; Amp. 5%, 10%, 30% - 1ml sol. ol.
	Vicasolum	Tab. 0,015; Amp. 1% - 1ml
	Videinum	Tab. 1500 UA

Hormones Drugs, Antagonists, and Other Agents Affecting Endocrine Function

Hormonal drugs are medicaments of hormones or their synthetic analogue. According to **chemical structures** they are divided into:

1. Drugs of peptide structure which interact with receptors of membranes
2. Drugs of steroid structures which interact with receptors inside of cells

According to their **origin** they are divided into:

1. Native hormones (insulin).
2. Synthetic analogues (prednisolone).

The hormone drugs:

They have no specificity (the drugs from animal tissues are used for treatment of people). They are not energetic or plastic substances. They may have permissive action in low doses and act on glands. They have pharmacodynamic actions. They have indications, adverse effects, contraindications. They are used for replacing therapy, stimulating therapy, inhibiting therapy

Mechanism of action: Many hormones affect signal transduction through one of three major mechanisms. **Cyclic adenosine monophosphate** (cyclic AMP), or the **second messenger**, is increased via adenylyl cyclase; cyclic AMP activates protein kinases, which phosphorylates cellular constituents. Calcium (Ca^{2+}) levels are also affected. It appears that guanine nucleotide proteins (G proteins) may activate membrane-bound phospholipase C and account for the increased membrane fluidity, Ca^{2+} flux, and "flip-flop" of lipids in the membrane bilayer.

Insulin and certain growth factors may act as membrane-bound receptors, which are also protein kinases. Steroid hormones bind to a membrane-bound receptor and become internalized via endocytosis. These hormone-receptor complexes access cytosolic or nuclear receptor proteins to act on DNA. **Feedback inhibition** of hormone synthesis and release can be manipulated for therapeutic goals or used diagnostically to determine the level of endocrine dysfunction.

Hypothalamic hormones' drugs

Sermorelinum - Growth Hormone-Releasing Hormone (GHRH) drug are available for Therapeutic uses: In normal individuals, produce a rapid increase in plasma growth hormone levels; their primary use is to determine the cause of growth hormone deficiency.

Somatostatin (Somatotropin Release-Inhibiting Hormone; SRIF) is of no clinical value because of its short duration of action. **Octreotidum**, a synthetic octapeptide somatostatin analogue with a longer duration of action has been found useful in the management of acromegaly, carcinoid, gastrinoma, glucagonoma, and other endocrine tumors.

Protirelinum (Rifatyronum) - Thyrotropin-Releasing Hormone (TRH) stimulates release of thyrotropin from the anterior pituitary. TRH also increases prolactin production but has no effect on the release of growth hormone or ACTH. It is used for thyroid function diagnostics.

Corticotropin-Releasing Hormone (CRH) stimulates secretion of both ACTH and beta-endorphin (a closely related peptide) from the pituitary. CRH can be used in the diagnosis of abnormalities of ACTH secretion. It is used for investigation now.

Gonadotropin-Releasing Hormone (GnRH or LHRH): GnRH is a decapeptide; leuprolidum is a synthetic nonapeptide with, similar activity. When given in pulsatile doses (resembling physiologic cycling), these agents stimulate gonadotropin release. In contrast, steady dosing causes a marked inhibition of gonadotropin release – in effect, a medical castration. GnRH is used in the diagnosis and treatment (by pulsatile administration) of hypogonadal states in female and male patients. Leuprolidum and several analogues (short acting agents - **nafarelinum, gosarelinum, and buserelinum and their depot-forms**) are used to suppress gonadotropin secretion (by administration in steady dosage) in patients with prostatic carcinoma or other gonadal steroid-sensitive tumors, endometriosis, or precocious puberty. GnRH agonists are also used to suppress endogenous gonadotropin release in women who are undergoing controlled ovarian hyperstimulation and in assisted reproduction technology (e.g. in vitro fertilization).

Prolactin-Inhibiting Hormone (PIH, Dopamine): Dopamine is the physiologic inhibitor of prolactin release. Because of its peripheral effects and the need for parenteral administration, dopamine is not useful in the control of hyperprolactinemia, but bromocriptine and other orally active ergot derivatives (e.g. cabergoline, pergolide) are effective in reducing prolactin secretion from the normal gland as well as from pituitary tumors.

Pituitary hormones

Anterior Pituitary hormones include growth hormone (GH, somatotropin); thyroid-stimulating hormone (TSH, thyrotropin); adrenocorticotropin (ACTH); follicle-stimulating hormone (FSH); luteinizing hormone (LH); prolactin (PRL).

Corticotropin is a drug of adrenocorticotropic hormone.

Pharmacokinetics: Corticotropin is administered intravenously or intramuscularly. Length of action is near 4-6 hours.

Pharmacodynamics: Corticotropin stimulates cortex of adrenal, has anti-inflammatory, antiallergic influence and stimulates catabolism more than anabolism, may influence on lipolysis, lipogenesis, gluconeogenesis and glycogenolysis.

Therapeutic use: Protection of trophic and adrenal cortex, during corticosteroid

therapy.

Adverse effects: Diabetogenic action, delays sodium and water, increases arterial pressure, mass, releases calcium from bones. Increases of gastric secretion, excitaion.

Drugs of Growth Hormone (Somatotropin) influence on statural growth, as well as balanced systemic growth. Retention of protoplasmic nitrogen, increased amino acid transport, and decreased plasma urea levels. Growth hormone may act by stimulating synthesis or release of **somatomedins**, which are identical to polypeptides known as **insulin-like growth factors (IGF) 1 and 2**. IGF-1 appears to mediate growth hormone activity, enhancing sulfate incorporation into proteoglycans, increasing protein synthesis, RNA, and DNA. **Adverse reactions.** Occasional headache, myalgia, mild hyperglycemia, and glucosuria. Leukemia in a small percentage of treated children. Hypothyroidism. Glucose intolerance due to insulin resistance. Reduction of growth-promoting effects as a result of interference from glucocorticoid therapy. Development of a limp due to slipped capital femoral epiphysis.

Hypersecretion of growth hormone can result in **acromegaly** and **gigantism**.

The use of **bromocriptine**, a dopaminergic agonist, in acromegaly is paradoxical since dopamine stimulates growth hormone secretion in normal individuals. Analogues of somatostatin, such as **octreotide**, offer therapeutic promise with minimal side effects.

Prolactin is not used in therapy now.

Drugs of Gonadotropic hormones, FSH, LH, hCG, and inhibin, are also collectively known as glycoprotein hormones.

Follicle-Stimulating Hormone (FSH): FSH is a glycoprotein which stimulates gematogenesis and follicle development in women and spermatogenesis in men. The preparation usually used is **urofollitropinum**, a product extracted from the urine of postmenopausal women.

Luteinizing Hormone (LH): LH is the major stimulant of gonadal steroid production. In women, LH also regulates follicular development and ovulation. No

pure preparation of LH is currently in use. **Human chorionic gonadotropin (hCG)**, which has an almost identical structure, is used in place of LH for treatment of hypogonadism in men and women and as part of controlled ovarian hyperstimulation and assisted reproductive technology programs.

Menotropinum: Menotropinum are human menopausal gonadotropins which consist of FSH and LH from the urine of postmenopausal women. The product is often used in combination with human chorionic gonadotropin in the treatment of hypogonadal states and as part of controlled ovarian hyperstimulation and assisted reproductive technology programs.

The increase of gonadotropin release may be achieved with clomipheni citras. The antagonist of gonadotropin release is **danazolium**.

Thyroid-Stimulating Hormone (TSH): In thyroid cells, this peptide increases iodine uptake and production of thyroid hormones. TSH has been used as a diagnostic tool to distinguish primary from secondary hypothyroidism.

Posterior Pituitary hormones

Oxytocinum: Oxytocinum is a nonapeptide synthesized in cell bodies in the paraventricular nuclei of the hypothalamus and transported through the axons of these cells to the posterior pituitary, where the peptide is released into the circulation. Oxytocinum is an effective stimulant of uterine contraction and is often used intravenously to induce or reinforce labor. Because it causes contraction of smooth muscle in the myoepithelial cells of the mammary gland, oxytocin also can be used by lactating women as a nasal spray to stimulate milk let-down.

Vasopressinum (Antidiuretic Hormone, ADH): Vasopressinum is synthesized in the supraoptic nuclei of the hypothalamus and released from the posterior pituitary. Vasopressinum acts on V_2 receptors and increases the synthesis or insertion of water channels by a cAMP-dependent mechanism, resulting in an increase in water permeability in the collecting tubules of the kidney. The increased water permeability permits water reabsorption into the hypertonic renal papilla, thus causing the antidiuretic effect. Vasopressinum also causes smooth muscle contraction (a V_1 effect). **Desmopressinum**, a selective agonist of V_2 receptors, is used in the treatment

of pituitary diabetes insipidus.

There are drugs containing both vasopressin and oxytocin – **pituitrinum and adiurectinum**. Pituitrinum is an aqueous extract, it is introduced intramuscularly and subcutaneously in the treatment of diabetes insipidus, in obstetrical practice.. Adiurectinum is used for the treatment of diabetes insipidus only.

Thyroid hormones

There are two active forms of thyroid hormone: **thyroxine (T₄)** and **triiodothyronine (T₃)**, which is the more potent form. **Levothyroxinum and triiodthyroninum** are according drug forms.

Mechanisms of Action of Thyroxine and Triiodothyronine: T₃ is about ten times more potent than T₄; since T₄ is converted to T₃ in target cells, the liver, and the kidneys, most of the effect of circulating T₄ is probably due to T₃. Thyroid hormone binds to receptors in the nucleus which control the expression of genes responsible for many metabolic processes. The T₃ receptor exists in two monomeric forms: alpha and beta. When activated by T₃, the alpha and beta monomers combine to form $\alpha\alpha$, $\beta\beta$, $\alpha\beta$ dimers. These T₃-activated dimers bind to DNA response elements and control the synthesis of RNA, which codes for specific proteins which mediate the actions of thyroid hormones.

The proteins synthesized under T₃ control differ depending upon the tissue involved; these proteins include Na⁺/K⁺ ATPase, specific contractile proteins in smooth muscle and the heart, enzymes involved in lipid metabolism, important developmental components in the brain, etc. T₃ may also have a separate membrane receptor-mediated effect in some tissues.

Pharmacologic effects: The organ level actions of the thyroid drugs include normal growth and development of the nervous, skeletal, and reproductive systems and control of metabolism of fats, carbohydrates, proteins, and vitamins. Thyroid hormones regulate growth and development.

Therapeutic uses: Thyroid hormone therapy is used for the treatment of hypothyroidism (myxedema), including myxedema coma. If thyroid hormone therapy is begun early after birth in hypothyroid infants, the consequences of cretinism are

prevented. Thyroid hormone is used in patients with simple goiter and in patients with nodular goiter who are deficient in the secretion of thyroid hormone. In the case of nodular goiter, carcinoma should be ruled out.

Adverse effects: Increase excitability, sweating, tremor. Cardiac effects are the most important and call for care in initiating therapy. Palpitations caused by thyroid hormones can be treated with β -adrenergic blocking agents. Levothyroxinum and triiodthyroninum can cause thyrotoxicosis. During long-term administration, serum T₄ levels may rise without a change in dose..

Thyroid hormone inhibitors

Iodide Salts and Iodine: Iodide salts inhibit organification (iodination of tyrosine) and thyroid hormone release; these salts also decrease the size and vascularity of the hyperplasic thyroid gland.

Radioactive Iodine: Radioactive iodine (¹³¹I) is taken up and concentrated in the thyroid gland so avidly that a dose large enough to severely damage the gland can be given without endangering other tissues. Unlike the thioamides and iodide salts, an effective dose of ¹³¹I can produce a permanent cure of thyrotoxicosis without surgery. ¹³¹I should not be used in pregnant or nursing women.

Thioamides: Mercazolilum (methimazolum), Propylthiouracilum (PTU) and are small sulfur-containing molecules which inhibit thyroid hormone production by several mechanisms. The most important effect is to block iodination of the tyrosine residues of thyroglobulin. In addition, these drugs may block coupling of DIT and MIT.

Therapeutic uses: Antithyroid agents are most frequently used to treat children, young adults and pregnant women with hyperthyreodism due to Graves' disease. They may be used: alone; with radioiodine, while awaiting the beneficial effects of radiation to appear; prior to the surgical treatment of hyperthyroidism.

Adverse effects: The most serious adverse effect, though rare, is agranulocytosis. The most common adverse effect is transient leucopenia. Other common complaints are maculopapular rash and fever. Joint pain and hair depigmentation can occur.

Parathyroid hormones

Parathyroidinum is the drug of parathyroid hormones which increases calcium transport and reabsorption and may rise blood pressure and is used rarely in hypoparathyroidism.

Calcitoninum

Calcitoninum, in part by a cyclic AMP-mediated reaction, increases kidney excretion of Ca^{2+} , phosphate, and sodium (Na^+).

Therapeutic uses: The major uses of calcitoninum are to decrease hypercalcemia and hyperphosphatemia in patients with: Hyperparathyroidism, Idiopathic hypercalcemia of pregnancy, Vitamin D intoxication, Osteolytic bone metastases, Calcitoninum may decrease the rate of bone loss in patients with postmenopausal osteoporosis. Though calcitonin is effective for the treatment of Paget's disease of bone, patients may become resistant to therapy in several months.

Adverse effects include occasional edema and nausea and the stimulation of antibody formation.

DIABETES MELLITUS AND INSULIN THERAPY

The most common pancreatic disease requiring pharmacologic therapy is diabetes mellitus, a deficiency of insulin production or effect. Diabetes is treated with several formulations of insulin (all administered parenterally at present) and with four types of oral antidiabetic agents. Glucagon, a hormone which affects the liver, cardiovascular system and gastrointestinal tract, can be used to treat severe hypoglycemia in diabetics.

General considerations

In 1921, Banting and Best extracted insulin from the pancreas and demonstrated its therapeutic effects in diabetic dogs and human subjects. It is important to remember that diabetes mellitus involves not only a deficiency of insulin but also an excess of certain other hormones, such as growth hormone, glucocorticoids, and glucagon. Thus, not only the pancreas is involved in glucose homeostasis, but also the anterior pituitary gland and the adrenal cortex.

Type I (juvenile-onset, insulin-dependent, IDDM) diabetes. In this type of

diabetes, there is no circulating insulin in the plasma and, thus, insulin replacement is required. There is complete failure of pancreatic β -cell function. The patient is prone to both hyperglycemia and ketoacidosis.

Type II (maturity-onset, non-insulin-dependent, NIDDM) diabetes. This type may be due to a defect in the receptor on the pancreatic β -cell membrane. In the earliest forms of the disease, there is a delay in the initial secretion of insulin after stimulation by glucose. Also, less insulin than normal is secreted at any given glucose concentration. The patient is not prone to ketoacidosis.

Insulin consists of two amino acid chains joined together by disulfide linkages; it has a molecular weight of about 6000. Pancreatic β -cells form insulin from a single-chain precursor, proinsulin, which possesses little biologic activity. Insulin can exist as a monomer, a dimer, or a hexamer consisting of three dimers. Two molecules of zinc are coordinated in the hexamer form. The biologically active form is thought to be the monomer. There are species variations in the amino acid sequence of insulin.

Mechanism of action: The initial action of insulin is at the cell surface, where the hormone interacts with a highly specific receptor. Insulin facilitates the transport of glucose and amino acids.

Pharmacological effects: Insulin has extremely important effects in almost every tissue of the body. The insulin receptor, a transmembrane tyrosine kinase, phosphorylates itself and a variety of intracellular proteins when activated by the hormone. The major target organs for insulin action include the following: **Liver:** Insulin increases the storage of glucose as glycogen in the liver. Insulin also decreases protein catabolism. **Muscle:** Insulin stimulates glycogen synthesis and protein synthesis. **Adipose tissue:** Insulin facilitates triglyceride storage by activating plasma lipoprotein lipase, by increasing glucose transport into and by reducing intracellular lipolysis.

Pharmacokinetics: Regulation of insulin secretion. Insulin is synthesized in the β -cells of the islets of Langerhans as a single polypeptide precursor, preproinsulin, which is subsequently converted to proinsulin. Proinsulin is synthesized in the rough

endoplasmic reticulum and packaged, through the Golgi apparatus, into secretory granules. Along the way an enzymatic process converts proinsulin to insulin and C peptide. Stored granules containing many insulin molecules are released by exocytosis. Oral glucose has a greater ability to stimulate insulin secretion than intravenously administered glucose. Fatty acids, amino acids, and ketone bodies all increase insulin secretion. Gastrointestinal hormones, such as secretin, pancreozymin, and gastrin, can stimulate insulin secretion.

Preparations. Various types of insulin are made which differ in their onset and duration of action. The potency of insulin is expressed in USP units.

1. Crystalline zinc insulin (regular insulin).

Regular insulin is a short-acting, soluble insulin, which is prepared in a phosphate buffer with zinc at a pH of 3.5. Its peak action occurs in 2-4 hours and its duration is 5-7 hours. It can be administered subcutaneously or intravenously and is a good agent for exerting rapid control for diabetic ketoacidosis. The frequency of injections (4-5/day) is not very convenient.

2. Suspension zinc insulin.

Adding the basic protein protamine to crystalline zinc insulin causes the formation of large crystals. This produces a compound which is less soluble. When injected, this formulation serves as a tissue depot, producing slow absorption into the bloodstream. The action of protamine zinc insulin peaks in 16-18 hours and lasts up to 36 hours. Fine control of hyperglycemia is difficult with such a long-acting preparation.

3. Isophane insulin (NPH, neutral protamine Hagedorn).

This intermediate-acting insulin is similar to protamine zinc insulin, but it contains only a small amount of protamine (0.5 mg/100 units of insulin). Therefore, NPH insulin has an earlier onset and earlier peak effects than protamine zinc insulin, but the duration of action is similar for both preparations. The effects of NPH insulin peak in 8-12 hours and have a duration of 24-48 hours. These effects are clinically equivalent to combining 2-3 units of crystalline zinc insulin with 1 unit of protamine zinc insulin.

4. Lente insulins.

These insulins do not contain protamine; their insolubility results from the addition of excess zinc in an acetate rather than a phosphate buffer. The onset of action for the lente insulins varies greatly and depends upon the physical state, the ambient zinc concentration, and the pH. A microamorphous crystalline form, known as prompt insulin zinc suspension (semilente insulin), peaks in 4—8 hours and has a duration of action of 12-16 hours. A large crystalline form with a high zinc content, known as extended insulin zinc suspension (ultralente insulin), has an onset and duration of action similar to those of protamine zinc insulin. Combining 7 parts of ultralente with 3 parts of semilente produces insulin zinc suspension (lente insulin), which is quite similar to NPH insulin in its onset and duration of action.

5. Human insulins.

Human insulins are produced by semisynthetic and recombinant DNA techniques. Recently the human proinsulin gene was synthesized, and human proinsulin is now produced on a large scale as the precursor to human insulin. Biologic activity and intravenous pharmacokinetics of human insulins are quite similar to porcine insulin. Human insulins are useful for individuals with an allergy to insulin from animal sources. It is absorbed more quickly than porcine insulin after subcutaneous injection, thereby improving glycemic control after meals.

Ultra rapid and very short action: Insulin lispro is a recombinant human insulin which contains a transposition of two amino acids, lysine and proline. This transposition alters the physical properties of the peptide so that insulin lispro dissolves more rapidly at its site of administration and enters the circulation approximately twice as fast as regular crystalline insulin. It is considered ultra-rapid in onset and is suitable for use immediately before meals. Unlike other insulin preparations, increasing the dose only increases the intensity, not the duration of effect.

Rapid onset and short action: Crystalline zinc (regular) insulin, a rapid onset preparation, is used intravenously in emergencies, or administered subcutaneously in ordinary maintenance regimens, alone or mixed with intermediate- or long-acting

preparations. Before the development of insulin lispro it was the primary rapid onset agent for use in tight control regimens but required administration an hour or more before each meal.

Intermediate onset and action: These preparations include isophane insulin suspension (NPH insulin) and long suspension. Both preparations are given by subcutaneous injection; they are not suitable for intravenous use. When mixing intermediate onset insulin with regular insulin, NPH insulin is preferred because long insulin can retard the onset of action of regular insulin.

Slow onset and long action: Ultralente insulin is a long-acting insulin. It usually is given in the morning only, or morning and evening to provide maintenance or basal levels for 12-24 hours. This basal insulin level may be supplemented with injections of insulin lispro or regular insulin during the day to meet the requirements of carbohydrate intake. Insulin glargine, a modified form of human insulin, is an ultra-long-acting preparation which provides a peakless basal insulin level which lasts more than 24 hours. Protamine *zinc* insulin is another long-acting preparation.

Adverse effects: Hypoglycemia. The worst sequela is insulin shock, characterized by abnormalities of the CNS, including hypoglycemic convulsions. Early symptoms of hypoglycemia, such as sweating, tachycardia, and hunger, are thought to be brought about by the compensatory secretion of epinephrine. Hypoglycemia is best treated by administering glucose intravenously, or by giving fruit juice or other soluble carbohydrates. Glucagon may be administered parenterally as an alternative to glucose. **Local reactions.** Irritation at the site of insulin injection can lead to lipohypertrophy or lipoatrophy. Sites of injection should be changed. Subcutaneous infusion can result in infection and local allergic reactions to components of the infusion system. **Antigenic response.** With the development of new, more highly purified animal insulins and the advent of human insulin, the production of insulin antibodies and the hypersensitivity reactions are less of a problem. Insulin antibodies may attenuate responses to regular insulin injected subcutaneously and delay recovery from hypoglycemia. Antigenicity increases as the duration of action of the insulin is increased. **Growth-promoting properties** of

insulin may be a factor in the macrovascular complications of diabetes. **Weight gain** is an undesirable effect of intensive insulin therapy.

ORAL HYPOGLYCEMIC AGENTS (SULFONYLUREAS)

Four major groups of drugs are used for the oral treatment of diabetes: **insulin secretagogues, the biguanides, the thiazolidinediones, and the α -glucosidase inhibitors.**

Mechanism of action: Sulfonylureas stimulate insulin secretion from pancreatic β cells without entering the cell. This occurs in the absence of glucose. Sulfonylureas may also sensitize the pancreatic β cells to glucose and inhibit the efflux of K^+ from pancreatic β cells. Sulfonylureas induce increased activity of peripheral insulin intracellular receptors. Sulfonylureas may act to reduce glucagon secretion. High-affinity sulfonylurea receptors have been demonstrated on pancreatic β -cells. The order of potency of sulfonylurea in binding to β -cells approximates its potency in stimulating the release of insulin and inhibiting the effects of K^+ .

Pharmacokinetics: All sulfonylurea agents are readily absorbed from the small intestine and are avidly bound by plasma proteins. Their onset of action varies from 30 minutes to 3 hours. The duration of action also varies from agent to agent.

Mechanism of action: The primary action of the insulin secretagogues is to stimulate the release of endogenous insulin. All but one of the insulin secretagogues are sulfonylureas. The sulfonylureas close potassium channels in the pancreatic β -cell membrane; channel closure depolarizes the cell and depolarization triggers insulin release. Insulin secretagogues are not effective in patients who lack functional beta cells. These drugs may also reduce glucagon release and increase the number of functional insulin receptors in peripheral tissues. The "second-generation" sulfonylureas (**glibenclamidum, gliclazidum, gliquidonum, glipizidum, and glimepiridum**) are considerably more potent and used much more commonly than the older agents (**tolbutamidum, chlorpropamidum, tolazamidum, others**). The third generation includes 1 drug – **glimepiridum**.

Mechanism of action include blockade of ATP-dependent potassium channels

opening of the potential-dependent calcium channels. **Glimepiridum** does not influence this channels in heart and is less dangerous. Repaglinidum is a new insulin secretagogue from a chemical class known as the meglitinides. It also promotes insulin release by binding to potassium channels in pancreatic β -cell membranes. The most notable difference between repaglinidum and sulfonylureas is its rapid onset and short duration of action. It is taken just before meals for the purpose of controlling postprandial glucose concentrations.

Therapeutic uses: The sulfonylureas are used in the treatment of patients who have NIDDM and who cannot be treated with diet alone or who are unwilling to take insulin if dietary control fails. Though controversial, support the above statement, and many physicians have had success using the sulfonylurea agents. Combining a sulfonylurea with a suboptimal insulin regimen in patients with NIDDM may provide better glycemia control than the suboptimal insulin regimen alone or reduced insulin requirements.

Adverse effects:

Hypoglycemia can occur in elderly patients with hepatic or renal insufficiency because the agent will have a longer than expected duration of action. Its frequency is related to potency and duration of action of the drug. Cutaneous reactions include rashes and photosensitivity. Gastrointestinal reactions include nausea and vomiting. Hematologic reactions – leukopenia, agranulocytosis, thrombocytopenia, pancytopenia, and hemolytic anemia – occur. Transient cholestatic jaundice occurs rarely. Inappropriate secretion of antidiuretic hormone has been observed. A disulfiram-like reaction has been reported.

Biguanides: The biguanides act by reducing postprandial and fasting glucose levels in patients with type 2 diabetes. Their effects do not depend upon functional islet cells. Proposed mechanisms for their action include reduced hepatic gluconeogenesis, stimulation of glycolysis in peripheral tissues, reduction of glucose absorption from the gastrointestinal tract, and reduction of plasma glucagon levels. Several biguanides are in use abroad. **Metforminum** is the primary member of this group. Unlike the sulfonylureas, the biguanides do not cause hypoglycemia. Their

most common toxicity is gastrointestinal distress (nausea, diarrhea), and they can cause lactic acidosis, especially in patients with renal or liver disease, alcoholism, or conditions which predispose to tissue anoxia (e.g. chronic cardiopulmonary dysfunction). Metformin also inhibits vitamin B₁₂ absorption.

Adverse effects: hypoglycemia, dyspepsia, metallic taste, and acidosis.

Thiazolidinediones:

Mechanism and pharmacological effects: Thiazolidinediones increase target tissue sensitivity to insulin. **Troglitazone** was the first thiazolidinedione introduced, but it was removed from the market in several countries because of hepatotoxicity. **Rosiglitazone and pioglitazone** appear to carry less risk of serious liver dysfunction. The mechanism of action of the thiazolidinediones is not fully understood but they stimulate the peroxisome proliferator-activated receptor-gamma nuclear receptor (PPAR- γ receptor). This nuclear receptor regulates the transcription of genes encoding proteins involved in carbohydrate and lipid metabolism. The "glitazones" increase glucose uptake in muscle and adipose tissue, inhibit hepatic gluconeogenesis, and have effects on lipid metabolism and the distribution of body fat. Thiazolidinediones reduce both fasting and postprandial hyperglycemia. They are used as monotherapy or in combination with insulin or other oral antidiabetic drugs.

Adverse effects: When these drugs are used alone, hypoglycemia is extremely rare. Thiazolidinediones can cause edema and mild anemia. Pioglitazone and troglitazone appear to induce cytochrome P450 (especially the 3A4 isozyme) and can reduce the serum concentrations of drugs which are metabolized by these enzymes (e.g. oral contraceptives, cyclosporin).

α -Glucosidase Inhibitors: **Acarbosa and miglitolum** are carbohydrate analogues which act within the intestine to inhibit α -glucosidase, an enzyme necessary for the conversion of complex starches, oligosaccharides, and disaccharides to the monosaccharides which can be transported out of the intestinal lumen and into the bloodstream. As a result of slowed absorption, postprandial hyperglycemia is reduced. They have no effect on fasting blood sugar. Both drugs can be used as

monotherapy or in combination with other antidiabetic drugs. Their primary adverse effects include flatulence, diarrhea and abdominal pain resulting from increased fermentation of unabsorbed carbohydrate by bacteria in the colon.

Adrenal corticosteroids drugs

The corticosteroids are those steroid hormones produced by the adrenal cortex. They consist of two major physiologic and pharmacologic groups: (1) glucocorticoids, which have important effects on intermediary metabolism, catabolism, immune responses, and inflammation; and (2) mineralocorticoids, which regulate sodium and potassium reabsorption in the collecting tubules of the kidney. This chapter reviews the glucocorticoids, the mineralocorticoids, and the adrenocorticosteroid antagonists.

Mechanism of action

Corticosteroids enter the cell and bind to cytosolic receptors which transport the steroid into the nucleus. The steroid-receptor complex alters gene expression by binding to glucocorticoid response elements (GREs) or mineralocorticoid-specific elements. Tissue-specific responses to steroids are made possible by the presence in each tissue of different protein regulators which control the interaction between the hormone-receptor complex and particular response elements.

Glucocorticoids stimulate gluconeogenesis. As a result, blood sugar rises, muscle protein is catabolized, and insulin secretion is stimulated. Both lipolysis and lipogenesis are stimulated, with a net increase of fat deposition in certain areas, e.g. the face (moon facies) and the shoulders and back (buffalo hump).

The steroid receptor is nuclear, not cytoplasmic as was previously thought. Once the steroid traverses the cell membrane and binds to the receptor, the steroid-receptor complex in the cell nucleus then binds to chromatin. The drug-receptor-chromatin complex stimulates the formation of messenger RNA (mRNA). The mRNA stimulates the synthesis of enzymes which control rate-limiting reactions in the synthetic pathway of the steroids.

Pharmacokinetics: Adrenal corticosteroids are readily absorbed from the gastrointestinal tract. Some 90% of a dose becomes bound to plasma proteins.

Steroids are metabolized in the liver and are often bioactivated by reduction reactions. The final or phase II metabolic reaction results in the conjugation of the steroid with sulfate or glucuronide and the conjugate then is excreted by the kidney.

Pharmacological effects: Corticosteroids cause increased liver glycogen stores, increased gluconeogenesis, increased lipolysis, the CNS effects, at times including euphoria, maintenance of cardiovascular function by potentiation of norepinephrine, Maintenance of skeletal muscle function (in Addison's disease, there is wasting of skeletal muscle), Increased hemoglobin synthesis, resulting in an elevation of the red blood cell count. They administration can result in anti-inflammatory and antiallergic effects, in which steroids suppress leukocyte migration, stabilize lysosomal membranes, reduce the activity of fibroblasts, which are involved in collagen and tissue repair in inflamed areas, reverse the capillary permeability which is associated with histamine release, suppress the immune response by inhibiting antibody synthesis, inhibition of growth and cell division

Glucocorticoids cause muscle protein catabolism. In addition, lymphoid and connective tissue, fat, and skin undergo wasting under the influence of high concentrations of these steroids. Catabolic effects on bone can lead to osteoporosis. In children, growth is inhibited.

Glucocorticoids have **immunosuppressive effects**, inhibit some of the mechanism involved in cell-mediated immunologic functions, especially those dependent on lymphocytes. These agents are actively lymphotoxic and are important in the treatment of hematologic cancers. The drugs do not interfere with the development of normal acquired immunity but delay rejection reactions in patients with organ transplants.

Glucocorticoids have **anti-inflammatory effects**, a negative effect on the distribution and function of leukocytes. These drugs increase neutrophils and decrease lymphocytes, eosinophils, basophils, and monocytes. The migration of leukocytes is also inhibited. The biochemical mechanisms underlying these cellular effects include the induced synthesis of an inhibitor of phospholipase A₂, decreased mRNA for COX-2, decreases in IL2 and IL3, and decreases in platelet activating

factor (PAF), an inflammatory cytokine.

Glucocorticoids such as hydrocortisonum are required for normal renal excretion of water loads. The glucocorticoids also have effects on the CNS. When given in large doses (especially if given for long periods), these drugs may cause profound behavioral disturbances. Large doses stimulate gastric acid secretion and decrease resistance to ulcer formation.

The major natural glucocorticoid is cortisol (hydrocortisonum).

Synthetic glucocorticoids: The mechanism of action of these agents is identical to that of hydrocortisonum. A large number are available for use; prednisolonum, dexamethasonum, and triamcinolonum are representative. Their properties (when compared to hydrocortisonum) include longer half-life and duration of action, reduced salt-retaining effect, and better penetration of lipid barriers for topical activity. They have more anti-inflammatory and antiallergic action.

Special glucocorticoids have been developed for use in asthma and other conditions in which good surface activity on mucous membranes or skin is needed and systemic effects are to be avoided. **Beclomethasoni dipropionas** and **budesonidum** readily penetrate into the airway mucosa but have very short half-lives after they enter the blood, so that systemic effects and toxicity are greatly reduced.

Therapeutic uses: Glucocorticoids are necessary in acute adrenal insufficiency associated with life-threatening shock, infection, or trauma. Glucocorticoids are also used in certain types of congenital adrenal hyperplasia, in which synthesis of abnormal forms of corticosteroids are stimulated by ACTH. they are used in inflammatory and allergic status (e.g. asthma, eczema, nephritis, organ transplant rejection, collagen diseases, and exophthalmos). Other applications include the treatment of hematopoietic cancers, neurologic disorders, chemotherapy-induced vomiting, hypercalcemia, and mountain sickness. Betamethasone, a glucocorticoid with a low degree of protein binding, is given to pregnant women in premature labour to hasten maturation of the fetal lungs. The degree of benefit differs considerably in different disorders and the toxicity of corticosteroids given chronically limits their use.

Mineralocorticoid effects: Mineralocorticoids cause retention of Na^+ , phosphate, Ca^+ , and bicarbonate (HCO_3^-) and reduction of serum K^+ . Control of serum Na^+ depends primarily upon the juxtaglomerular apparatus, where a low Na^+ level in the blood causes the release of renin from the kidney. Renin cleaves angiotensinogen to form angiotensin; angiotensin II triggers aldosterone release. Aldosterone acts on Na^+ and K^+ transport in the distal tubule of the kidney to enhance Na^+ reabsorption.

Desoxycorticosteronum and **fludrocortisonum** are the agents used as replacements for aldosterone in Addison's disease.

Adverse effects: Prolonged therapy with corticosteroids can result in the following: suppression of pituitary-adrenal function, increased susceptibility to infection, peptic ulceration, which may be the result of altered mucosal defense mechanisms, myopathy characterized by proximal arm and leg weakness, psychological disturbances, including suicidal tendencies or "steroid psychosis", posterior subcapsular cataracts, especially in children, osteoporosis, which can lead to vertebral fractures, glucocorticoids directly inhibit osteoblast formation as well as intestinal Ca^{2+} absorption. They also increase secretion of parathyroid hormone. Hyperglycemia. Glucocorticoids can arrest growth in small children receiving small doses. Both DNA synthesis and cell division are inhibited. The adverse effects of mineralocorticoids are edemas, increase of arterial pressure.

Androgens and antiandrogens

Testosteronum is synthesized in the testis, ovary, and adrenal cortex. It is the main drug for parenteral administration. Toestenatum is a prolonged form for parenteral administration. Methyltestosteronum is administered orally.

In target tissues, like the seminiferous tubules or Sertoli cells, testosterone is reduced to dihydrotestosterone. The actions of the androgenic hormones manifest in early embryonic growth (sex differentiation), early neonatal life (anabolic growth), puberty, and adult sexual life. The gonadotropin, LH, appears to mediate its effect through cyclic AMP on the Leydig cells to convert cholesterol to androgens. The major effect of FSH is on the Sertoli cells of the seminiferous tubules and, thus,

spermatogenesis. FSH also affects LH-mediated actions on the Leydig cells. Growth hormone and estrogen may have synergistic and antagonistic actions, respectively, on LH-mediated effects.

Many androgens have been synthesized in an effort to increase the anabolic effect without increasing androgenic action.

Mechanism of Action: Like other steroid hormones, androgens enter cells and bind to cytosolic receptors. The hormone-receptor complex enters the nucleus and modulates the expression of certain genes.

Pharmacodynamics: Testosterone is necessary for normal development of the male fetus and infant and is responsible for the major changes in the male at puberty (growth of penis, larynx, and skeleton; development of facial, pubic, and axillary hair; darkening of skin; enlargement of muscle mass). After puberty, testosterone acts to maintain secondary sex characteristics, fertility and libido. It also acts upon hair cells to cause male-pattern baldness. The major effect of androgenic hormones – in addition to development and maintenance of normal male characteristics – is an anabolic action which involves increased muscle size and strength and increased red blood cell production. Excretion of urea nitrogen is reduced, and nitrogen balance becomes more positive. Testosterone also helps maintain normal bone density.

Therapeutic uses: The primary therapeutic uses of the androgens is for replacement therapy in hypogonadism. They have also been used to stimulate red blood cell production in certain anemias and to promote weight gain in patients with wasting syndromes (e.g. AIDS patients). For desired anabolic effects (weight gain) in undernourished patients or in the terminally ill (this application is a controversial and dangerous form of abuse among professional athletes.) Replacement therapy in women with hypopituitarism; androgens are given in conjunction with other hormones (i.e. thyroid, growth, adrenal corticosteroid, and estrogen hormones). Breast cancer therapy due to an antiestrogenic effect. Short stature, not due to pituitary insufficiency (growth hormone) (Androgen treatment in children less than 9 years old may have negative consequences.) Hereditary angioneurotic edema, a condition where complement activation is unopposed, leading to increased vascular

permeability and angioedema.

Adverse effects: Acne, facial hair, and deepening of the voice in women. Menstrual irregularities. Male-pattern baldness, altered musculature, and hypertrophy of the clitoris. Premature closing of epiphyseal plates and altered bone development in children. Masculinization of the female embryo after in utero exposure. Inhibition of gonadotropin release (in normal men) and reduction spermatogenesis for months after discontinuation.

Feminizing effects: Gynecomastia in men but the mechanism is poorly understood. Exacerbation of feminizing effects in children and men with poor liver function.

Edema. Jaundice and cholestatic hepatitis, especially with all of the 17-a alkyl substituted androgens. Peliosis hepatitis (rare). Hepatic carcinoma. Effects on laboratory and diagnostic tests.

Antiandrogens

Androgen receptor antagonists, like cyproteronum and flutamidum, are potentially useful in treating prostate cancer, acne, male-pattern baldness, virilizing syndromes, precocious puberty, and inhibiting the sex drive in men who are sex offenders.

Finazteridum, a 5α -reductase inhibitor, acts by blocking the metabolic activation of testosterone to dihydrotestosterone. This agent is being studied in benign prostatic hypertrophy.

Receptor Inhibitors: Flutamidum and related drugs are nonsteroidal compounds which act as competitive antagonists at androgen receptors. These drugs are used to decrease the action of endogenous hormones in prostate carcinoma. **Cyproteronum** is a steroidal compound with the same action. The drug also has progestational activity which provides negative feedback to the pituitary. It is used for treatment of women with hirsutism. **Spirolactonum**, a drug used principally as a potassium-sparing diuretic, also inhibits androgen receptors and is sometimes used in the treatment of hirsutism.

Anabolic steroids

Anabolic steroids are the agents similar to androgens by the chemical structures, which have no androgenic effect, but have prominent anabolic effect. These drugs include phenobolinum, retabolilum, methandrostenolonum, oxandrolonum, and silabolinum etc.

Pharmacologic effects: Anabolic steroids activate the protein synthesis, appetite, promotes the weight gain, stimulate erythropoiesis, calcification of tissues, regeneration.

Therapeutical uses: Asthenia, osteoporosis, stimulation of regenerative processes, after radiotherapy, cachexia, long-term taking of glucocorticoides. Adverse effects. Dyspeptic disorders, damage of liver function, jaundice, edemas, in women – disorders of menstrual cycle depending of the voice, hirsutism.

Estrogens

The major ovarian estrogen in women is **estradiol**. The steroid has low oral bioavailability but is available in a micronized form for oral use. Estradiol can also be administered via transdermal patch, vaginal cream, or intramuscular injection.

The natural drugs are oestronum, and oestradioli dipropionas. Semisynthetic drug is aethinylestradiolum. Synthetic estrogens with high bioavailability (e.g. synoestrolum, mestranolum) are used in oral contraceptives.

Effects: Estrogen is essential for normal female sexual development. It is responsible for the growth of the genital structures (vagina, uterus, and uterine tubes) during childhood and for the appearance of secondary sexual characteristics and the growth spurt associated with puberty. It increases uterus sensitivity to oxytocinum and acetylcholinum. Estrogen has many metabolic effects: it modifies serum protein levels and reduces bone resorption, enhances the coagulability of blood and increases plasma triglyceride levels while reducing LDL cholesterol. Estrogen is also an effective feedback suppressant of pituitary FSH. It stimulates erythropoiesis, calcium transport.

Therapeutic uses: An important therapeutic use of estrogens is in the treatment of primary hypogonadism in young females. Another use is as hormone replacement therapy in women with estrogen deficiency due to premature ovarian failure,

menopause, or surgical removal of the ovaries. The HRT ameliorates hot flushes and atrophic changes in the urogenital tract. It is effective also in preventing bone loss and development of osteoporosis and may reduce the risk of coronary artery disease, memory loss, and Alzheimer's disease. The estrogens are very important as a component of oral contraceptives. They are also used in postcastration syndrome, amenorrhea.

Antiestrogenic agents

Clomiphene citrate, a partial agonist, is mainly an antagonist at pituitary estrogen receptors; this prevents negative feedback and increases the output of the pituitary gonadotropic hormones. It is used as ovulation inducing agent in anovulatory ovarian dysfunction and associated sterility. **Adverse effect** is hyperstimulation of the ovaries (pain in the hypogastrium, menorrhagia, thromboembolism, dyspeptic disorders). Tamoxifen is mainly an antagonist at estrogen receptors in the breast but acts as an agonist in bone. They reduce FSH and LH output from the pituitary by activating feedback receptors. Toremifene is more active than tamoxifen. They are used in cancer of the breast in postmenopausal women treatment. Raloxifene is used for prevention of osteoporosis in postmenopausal women. It has partial agonist effects on bone and increases serum HDL.

Gestagen agents (progestins)

1. Native gestagens of short action: Progesterone, Pregninone, and Utrogestanone.
2. Native gestagens of prolonged action: Oxyprogesterone caproate
3. Synthetic progesterone: Mifepristone (Mifeprex)

Progestins: Progesterone is the major progestin in humans. A micronized form is used orally for the HRT, and progesterone-containing vaginal creams are also available. Progestins cause development of secretory tissue in the breast and maturation of the uterine endometrium. They decrease uterus sensitivity to oxytocin. They have much less effect than the estrogens on plasma proteins but significantly affect carbohydrate metabolism and stimulate the deposition of fat. High doses inhibit the production of the FSH and thereby suppress ovarian function.

Therapeutic uses: A major therapeutic use of the progestins is as a component of oral or implantable contraceptives. They are used in the HRT to prevent estrogen-induced endometrial cancer. Large doses of medroxyprogesterone can be used to produce anovulation and amenorrhea in women with dysmenorrhea, endometriosis, or bleeding disorders. Urogestanum is used in recurrent abortions.

Adverse effects: Uterine bleeding, dyspeptic disorders, fever, decrease of arterial pressure. However, they may increase blood pressure and decrease high-density plasma lipoproteins (HDL). Long-term use of high doses is associated with reversible decrease in bone density and delayed resumption of ovulation after termination of therapy.

Antiprogestins, such as mifepristone, are under clinical investigation for use as a contraceptive and abortifacient.

Mifepristone is a competitive antagonist at both progesterone and glucocorticoid receptors. Its actions include: inhibition of ovulation during the follicular phase by blocking hypothalamic-pituitary progesterone receptors, which suppresses midcycle gonadotropin release; during the luteal phase, inhibition of progesterone action on the uterus, which induces prostaglandin release from the endometrium; termination of pregnancy by facilitating luteolysis, menstruation, uterine motility, softening of the cervix, and detachment of the embryo.

Other indications - Noncontraceptive uses (estrogens and progestins) :

Prevention of heart attacks. Estrogens have a beneficial effect in postmenopausal women in reducing myocardial infarction morbidity and mortality. Estrogens have a deleterious effect, increasing risk in men and possibly in premenopausal women. Estrogens decrease the LDL and increase HDL levels; progestins have the opposite effect. Atherosclerosis is correlated with elevated LDL and lower HDL levels.

Postmenopausal osteoporosis. Osteoporosis is due to loss of both hydroxyapatite (calcium phosphate complexes) and protein matrix (colloid), resulting in compromised skeletal integrity. Several months of estrogen therapy may be necessary to effect a positive Ca^{2+} balance. Doses of 15-25 mg/day are required to

maintain or increase bone density. The positive effects may be rapidly lost when estrogen therapy is discontinued. The risk-to-benefit ratio is highest for women who have undergone hysterectomy or oophorectomy because endometrial carcinoma (from estrogens) is no longer an issue.

Estrogen replacement therapy. Estrogen during and after **menopause** is used to relieve vasomotor symptoms, hot flashes, and atrophic vaginitis. **Dysmenorrhea** can also be treated with a nonsteroidal anti-inflammatory drug (NSAID). Failure of **ovarian development** (dysgenesis) may result in dwarfism due to hypopituitarism. Estrogen therapy at puberty in combination with an androgen for growth spurt can satisfactorily emulate endogenous release.

Antineoplastic uses of certain hormones have evolved, allowing manipulation of cancer development. Progestins are used in endometrial, breast, and prostate carcinomas and in hypernephromas. Antiandrogens and DES are used in prostatic cancer.

Contraceptives

Combination preparations are the most common oral contraceptives used and contain both an **estrogen** and a **progestin**.

The estrogen is used in either **ethinyl estradiol** or **mestranol**.

The progestin is used is **norethindrone acetate**, or **norgestrel**, or **ethynodiol diacetate**.

The primary mechanism of action appears to be suppression of the midcycle surge of LH and FSH, thereby suppressing ovulation and ovarian follicle growth.

Monophasic contraceptives are as follows: **logest**, **zanin**, **marvelonum**, **mersilonum**, **phemodenum**, and **yarina**.

Sequential preparations (estrogen for 14-16 days followed by 5-6 days of combined estrogen and progestin) were removed from the market due to reports of increased incidence of endometrial tumors.

A **biphasic** or **triphasic** preparation, which replaces these, has a fixed estrogen level, but varies the progestin level to reflect changes in the menstrual

cycle. This approach may minimize "breakthrough" or irregular bleeding. Biphasic (atenovinum) and triphasic (triregonum, triquilarum, trisistonum) are more physiologic, less reliable.

Single-entity preparations: The "minipill" contains progestin alone and may act by thickening the consistency of cervical mucus, which is a barrier to sperm. It has a high failure rate and may cause irregular bleeding.

The drugs which contain microdoses of gestogenes are continuinum, exlutonum, norcolutum and microlutum.

Adverse effects. Estrogen increases the risk of thrombotic events, presumably by increasing levels of clotting factors and platelet aggregation. Thrombophlebitis and thromboembolism are significantly increased and appear to be estrogen dose-dependent. The incidence of cerebral and coronary thrombosis is increased and reflects age, smoking, hypertension, or other comorbid disease, and duration of estrogen therapy. Mortality may increase 15-18 times in women over 45 years old who smoke. The use of preparations with low estrogen (35 mg or less) and progestin decreases the risk of thrombotic events. The side effects are also cholestatic jaundice, uterine bleedings, increased skin pigmentation, acne, hirsutism, mastalgia, increase of body weight, prolonged amenorrhea after cessation of taking of the drugs. Moderate-to-severe hypertension occurs. Estrogen and progestin facilitate salt and water retention due to increased plasma renin and consequent angiotensin activity. The development of certain types of cancer has been studied with oral contraceptives, but actual culpability is clouded by the long latency period and multiple risk factors. Nausea, vomiting, breast tenderness, weight gain, dizziness, and headaches are all associated with oral contraceptive use. Depression, irritability, ocular disturbances, and an increased incidence of gallbladder disease have been noted. Oral contraceptives may cause birth defects if taken during the first trimester of pregnancy. Depot drugs are used for parenteral (**depo-provera**) and subcutaneous administration.

Levonorgestrel implants (Norplant)

Activity and Mechanism of action: Contraception is achieved by subdermal implantation of six flexible silastic tubes containing a progestin, levonorgestrel. Effective contraception may last up to 5 years.

The mechanism of action is due to inhibition of ovulation and thickening of cervical mucus. Effective contraception may be achieved within 1 day when implanted during the first 7 days of menstruation. Altered lipoprotein levels have been noted. Total cholesterol levels decreased in all studies and significantly so in several trials. High-density lipoprotein (HDL) levels have been noted both up or down but with no definite trend. Low-density lipoprotein (LDL) and triglyceride levels decreased. Increases have been noted in the ratio of total cholesterol to HDL-cholesterol, but they were not statistically significant.

Adverse effects. Bleeding irregularities are common but diminish over time; hemoglobin levels generally increase, probably due to diminished loss of menstrual blood. **Delayed follicular atresia** has been noted but rarely caused complications. **Increased weight** may increase the possibility of ectopic pregnancy. Patients with lower abdominal/pelvic pain should be evaluated to rule out ectopic pregnancy. Levonorgestrel has been identified in **breast milk**. Children followed up to 3 years show no significant effects on growth or health. Levonorgestrel implants or other steroids, are not the contraceptives of first choice for lactating mothers. **Thromboembolic disorders** may require removal of the steroid implants. Removal should also be considered in cases of prolonged immobilization or illness. Cardiovascular side effects are increased in women who smoke. Elevated blood pressure may occur. There is an increased risk of thrombosis, stroke, or heart attack. Carcinoma risk assessment may show reduced ovarian and endometrial cancer ratios but increased risk of breast cancer. Hepatic tumors have been reported. Ocular lesions have been reported.

Postcoital drugs. Postinorun contains Levonorgestrel in high doses. It is recommended after coitus. Mephipristonum is used also as postcoital drug.

There are also such drugs as:

1. Native estrogens: Oestronum, Oestradiolum
2. Half synthetic estrogen: Aethyhyloestradiolum
3. Synthetic estrogens: Synoestrolum

The ovary is the primary source of sex hormones in women during the child-bearing years, in between puberty and menopause. When properly regulated by FSH and LH from the pituitary, each menstrual cycle consists of the following events: A follicle in the ovary matures, secretes increasing amounts of estrogen, releases an ovum, and is transformed into a progesterone-secreting corpus luteum. If the ovum is not fertilized and implanted, the corpus luteum degenerates; the uterine endometrium (which has proliferated under the stimulation of estrogen and progesterone) is shed as part of the menstrual flow, and the cycle repeats. The mechanism of action of both estrogen and progesterone involves entry into cells, binding to cytosolic receptors, and translocation of the receptor-hormone complex into the nucleus, where it modulates gene expression.

Local contraceptives - pantetex, pharमतex, etc.

	Drug	Drug forms
1.	Corticotropinum	Flac.10, 20, 30, 40 UA
2.	Oxytocinum	Amp. 1ml (5UA)
3.	Triiodthyronini hydrochloridum	Tab. 0,00002, 0,00005
4.	Metforminum	Tab. 0,5
5.	L-Thyroxinum	Tab. 0,000005, 0,00001
6.	Mercazolilum	Tab. 0,005
7.	Parathyreoidinum	Amp. 1ml
8.	Insulinum pro Injectionibus	Flac. 5ml, 10ml (40UA, 80UA – 1ml)
9.	Suspension Zinc- Insulinum	Flac. 5ml (40UA – 1ml)
10.	Glibenclamidum	Tab. 0,005

11.	Metformini hydrochloridum	Tab. 0,5
12.	Acarbosa	Tab. 0,05, 0,1
13.	Aethyniloestradiolum	Tab. 0,00001, 0,00005
14.	Synoestrolum	Tab. 0,001
15.	Progesteronum	Amp. 1%, 2,5% - 1ml sol. ol.
16.	Oxyprogesteroni Caproas	Amp. 12,5%, 25% - 1ml sol. ol.
17.	Turinal	Tab. 0,005
18.	Oestronum	Amp. 0,05%, 0,1% - 1ml sol. ol. (5000, 10000UA– 1ml)
19.	Tamoxifenum	Tab. 0,01, 0,02
20.	Logest	Dragee №21
21.	Tri-regol	Tab. №63
22.	Postinor	Tab. №4
23.	Climonorm	Dragee №21, №63, №126
24.	Testosteroni Propionas	Amp. 1%, 5% - 1ml sol. ol.
25.	Retabolilum	Amp. 5% - 1ml sol. ol.
26.	Phenobolinum	Amp. 1%, 2,5% - 1ml sol. ol.
27.	Methandrostenolonum	Tab. 0,001, 0,005
28.	Desoxycorticosteroni Acetas	Tab. 0,005; Amp. 0,5% - 1ml sol. ol.
29.	Hydrocortisoni acetas	Susp. 2,5% - 5ml; Ung. 0,5%
30.	Prednisolonum	Tab. 0,005; Amp. 1ml (0,03); Guttas 0,3% - 5ml; Ung. 0,5% - 10, 20

31.	Methylprednisolonum	Tab. 0,004; Amp. 0,02, 0,04
32.	Dexamethasonum	Tab. 0,0005; Amp. 1ml (0,004)
33.	Triamcinolonum	Tab. 0,004
34.	Flumethasoni Pivalas	Ung. 0,02% - 15
35.	Beclomethasoni Dipropionas	Aerosol

Enzymes and inhibitors of enzymes

Enzymes drugs contain enzymes which play role of biological catalyzers of metabolism in organism. They are classified into:

1. Peptidases: pepsinum, succus gastricus naturalis, pepsidilum, acidin-pepsin. They tear peptide connections; normalize secretor and motor functions of stomach, intestines, liver, and kidney. They contain ingredients of digestive juices and are effective in the cases of diarrhea, hypoacidic, anacidic gastritis. Succus gastricus naturalis consists of all enzymes.

Therapeutic use: replacing therapy in achilia, hypo- and anacidic gastritis, dyspepsia.

2. Proteases: trypsinum crystallisatum, chimotrypsinum, chimopsinum. They tear peptide connections in protein molecules, split peptones and aminoacids. Major part of them is obtained from horned cattle, some of them from microorganisms (asperase etc), from plants (carycinase, lecozym).

Pancreatinum is enzyme drug from pancreas which contains lipase, amylase and trypsinum.

Therapeutic use: replacing therapy at insufficient function of pancreas, anacid gastritis, dyspepsia, and enterocolitis.

Adverse effects: aggravation of gout, allergy.

3. Nucleases: ribonucleasum, desoxyribonucleasum. These drugs are obtained from horned cattle. **Mechanism of action** is connected with depolymerization of

nucleinic acids to oligonucleotidis.

Pharmacodynamics, therapeutic uses are similar to proteases.

4. Drugs of gyaluronidase (lidasum, rodinasum).

Lidasum contains gyaluronidase, which depolymerizes gyaluronic acid and decreases its viscosity, increases tissues' permeability, penetration of other drugs.

Therapeutic use: contractures of joints, scars after burns operations, hematoma.

Adverse effects: allergic reactions.

5. Fibrinolytic drugs (streptolyasum, alteplasum-cutilise, inocinasum, fibrinolysinum).

6. Polyferment drugs of combine action.

6.1 Drugs of replacing therapy: pancreatinum, festalum, panzinorm forte, creonum, nigedasum, mezym forte. They are used in achilia, chronic pancreatitis, insufficiency of pancreas. They contain proteases in complex with bile, extracts from plants.

6.2 Drugs for systemic therapy (wobenzym, flogenzym, wobemugos). These drugs contain proteolytic enzymes of animals, plants and biological active substances. They have anti-inflammatory, analgetic, antiaggregative, immunomodulative, hypocholesterinemic, cardioprotective, anticancerogenic actions. They are used in therapy, surgery, hematology, oncology, stomatology, obstetrics and gynecology, cardiology, gastroenterology, sport medicine etc.

7. Others: L-asparaginasa, cytochromum C, penicillinasum, ubichinonum etc.

Inhibitors of enzymes

Inhibitors of enzymes inhibit activity of different enzymes. The main of them are classified into:

1. Inhibitors of proteinase: contrycalum.
2. Inhibitors of fibrinolysis: acidum aminocapronicum.
3. Anticholinesterase drugs: proserinum, physostigmini salicylas, galanthamini hydrobromidi, pyridostigmini bromidumum, phosphacolum.
4. MAO – inhibitors: nialamidum, pyrazidolum.
5. Carboanhydraze inhibitors: diacarbium.

6. Xantinoxydase inhibitors: allopurinolum.

7. Inhibitors of acetaldehydogenase: disulphyramum.

8. Inhibitors of HMG KoA-reductase: lovastatinum, simvastatinum, pravastatinum, fluvastatinum, atorvastatinum.

Acids and alkalines

For normal vitality of organism it is necessary to support the stability intrinsic environment – homeostasis and acid basic balance. There are drugs of acids and alkalines. Pharmacokinetics and pharmacodynamics of acids and alkalines are connected with their degree of dissociation in water solutions. They are divided into:

1. Acids

1.1 Inorganic acids: acidum hydrochloridum.

1.2 Organic (light) acids: lacticum, boricum, carbonic acids.

2. Compounds acids with alkaline properties (natrii hydrocarbonas, magnesi oxydum).

Acids

Pharmacokinetics: electroneutral molecules penetrate through cells membranes easily that is why acids dissociating weakly (acidum boricum) have prominent antimicrobial action. Acids are absorbed from stomach quickly. In blood they connect with hydrocarbonates and basic phosphates. CO₂ is formed and excreted through respiratory ways and acidic phosphates are excreted with urine.

Pharmacodynamics: Biological action is connected with dissociation. There are local and resorptive actions of acids. There are adstringent, irritative, cauterize, necrotic actions locally. They denature proteins, cause surface albuminates, promote adstringent effect, denature proteins, cause deep-cauterizing and coagulative necrosis. Damages of tissues by acids are accompanied by hyperemia, inflammation, edema etc. Acids may cause compensative or decompensative acidosis. Sometimes it is necessary to cause compensative acidosis in tetany, administration of some drugs (hexamethylentetraminum) with diuretics which cause alkalosis (thiazides, acidum etacrynicum).

Decompensative alkalosis is expressed by hypertension, seizures, suffocation,

coma, inhibition of respiration, collapse. Acids are used locally as antiseptic and disincentive drugs (acidum boricum), complex therapy of inflammatory diseases (acidum salicylicum), treatment of corns and warts, treatment of burn caused by acids. The drug of acids (acidum hydrochloridum dilutum) is administered orally in achylia, hypoachylia, for improvement of absorption drugs of iron. Acidum citricum is administered for removal of alkalosis.

In the cases of **acids intoxication** there are symptoms of their local action burns in gullet acute pains, vomiting, diarrhea and shock.

Treatment: Lavage with water, neutralization of acids (magnesii oxydum), eggs albumin, milk, narcotic analgetic, symptomatic therapy.

Acidum hydrochloricum dilutum (8,3%) creates the necessary concentration of hydrogenium for maximal activity of pepsin, transformation of pepsinogene into pepsin, rouses denaturation of proteins, realizes antimicrobial action. Acidum hydrochloricum dilutum is used for treatment of hypoacidic gastritis, achylia and with the drugs of iron.

Alkalines

Alkalines denaturate tissues proteins with formation of friable albuminates (colliquative necrosis). That is why locally they have irritative, cauterize necrotize actions. Drugs compounds with alkaline properties are used (magnesii oxydum, alumini hydroxydum, natrii hydrocarbonas, natrii tetraboras, calcii hydrocarbonas praecipitatus, magnesii subcarbonas). The alkalines have local and resorptive actions (antacid actions). They have also antimicrobial action. Resorptive action is connected with increase of decompensative alkalosis.

Therapeutic uses of alkalines for local therapy are: antiseptic and disinfectant drugs (natrii tetraloras, solutio Ammonii caustici); for diseases of local inflammatory and allergic reactions – pain itches, hyperemia, edema (natrii hydrocarbonas). For treatments of acid burns the alkaline drugs are administered orally in: at hyperacidic status – hyperacidic gastritis, ulcers (magnesii oxydum, Alumini hydroxydum, “Maalox”, “Almagel”); expectorants (natrii hydrocarbonas). The acids are administered parenterally for treatment of acidosis (natrii hydrocarbonas).

In the cases of **alkalines intoxication** it is observed – acute pain in mouth, gullet, stomach, intestines, nausea, vomiting with blood, excitation, headache, dizziness, seizures, fever, delay of respiration, decreases of reflexes, hyperesthesia, coma, yellow color of skin. **Treatment** consists of narcotic analgetics, mucilaginous lavage by water, parenterally by acidum litricum 1%, Solutio natrii chloridi isotonica.

Drugs of alkaline and alkaline-ground metals.

Classification:

1. Salts of alkaline metals;
 - 1.1. Salts of sodium - natrii chloridum;
 - 1.2. Salts of kalium – kalii chloridum;
2. Salts of alkaline grounds metals;
 - 2.1. Salts of calcium – calcii chloridum, calcii gluconas;
 - 2.2 Salts of magnesium – magnesii sulfas.

Ions of natrium influence on osmotic pressure, alkaline and volume of blood circulating. Extracellular ions takes part in polarization and depolarization processes of cell membrane and neurotransmission, provides constant osmotic pressure.

Natrii chloridi isotonica (0,9%) normalizes water-salts metabolism, osmotic pressure, ion compound, volume of blood, increases antitoxic properties of organism.

Natrii chloridum, hypertonic solution (2-10%) locally have antimicrobial properties, stimulates formation of granulations and dosing of wounds. Rectally it has drastic effect by means of receptors of intestines irritation.

Therapeutic use of sol. natrii chloridi isotonica: compensation of missing of fluids (dehydration in cases of vomiting, diarrhea, hemorrhage); forced diuresis; to dissolve other drugs; correction of water basic metabolism; irrigation of wounds.

Hypertonic solution of natrii chloridum are used locally of treatment of wounds, intravenously for stopping lung, stomach, uterine, bleeding. Hyponatremia. 2-5% sol. for lavage of stomach in the case of intoxication of argentum salts. Orally in patients with Addison disease

Potassium. Kalium ions (intracellular ions) take part in polarization – depolarization processes in cell membranes, in neurotransmission automatism.

Kalium influences on activity of $\text{Na}^+\text{-K}^+\text{-ATP-ase}$, synthesis of corticosteroids. Kalii chloridum is used in cases of hypokaliemia, which is viewed in the cases of diarrhea, vomiting, treatment of cardiac glycosides, glucocorticoids, mineralocorticoids, myorelaxants, cathartic drugs, and insulins; for treatment of arrhythmias, ischemic heart diseases, hypotrophy.

Calcium. Calcium regulates functions of the CNS, heart gastrointestinal tract, muscular system, blood coagulation, forms and saves structures of bones, diseases vessels permeability. Calcium activates phosphorus systems, forms bones tissue, activates actomyozine in smooth and skeletal muscles; stimulates catecholamines release from sympathetic nerve endings. Calcii chloridum, calcii gluconas, calcii lactas, calcii glycerophosphas are used in the cases of hypocalcemia, inflammations allergic nature edema, capillar bleeding, treatments of fractures, hyperkaliemia, tetanus, spasmophyllia, rachitis, osteoporosis, immobilization.

Magnesium. Intracellular ions take part in energetic processes, activates membranes $\text{Na}^+\text{-K}^+\text{-ATP-ase}$, depress catecholamines release from the sympathetic nerve endings. It has sedative, analgetic, anticonvulsive, hypotensive, cholekinetic, cholagogic, cathartic, tocolytic, spasmolytic actions.

Magnesii sulfas is used in hypertensive crises, convulsions, pregnancy therapy, intestinal paresis as cholagogic and choleckinetic means.

Drugs for transfusion therapy.

1. Plasma substitutes (Albuminum, Rheopolyglucinum, Gelatinosum, Reamberinum) restore volume of circulating blood, support colloid – osmotic pressure, increase AP, improve rheological blood properties.

2. Rehydration and desintoxication drugs which decrease intoxication effects, normalize hemodynamics are: glucosum, fructosum, natrii chloridum, disolum, lactosolum.

3. Drugs for acidosis which restore acid base balance correction:

Trisaminum, Natrii hydrocarbonas.

4. Drugs for intravenous nutrition: Aminosterilum, Aminotrophanum, Lipafundinum. These drugs consist of energy amino acids, essential fatty acids.

Isotonic solutions of glucose (5%) are used for increase volume of fluids, as energetic source. **Hypertonic solutions (40%)** promote increase of osmotic pressure, increase antitoxic liver function, improve contractions of heart, increase diuresis and cause vessels dilatiny, are antidote of insulin.

№	Drug	Drug forms
1.	Acidum Hydrochloricum dilutum	Solutio
2.	Natrii Hydrocarbonas	Pulv.; Tab. 0,5, 0,3; Amp. 4% - 20ml; supp. 0,3, 0,5
3.	Natrii Chloridum	Pulv.; Tab. 0,9; Amp. 0,9% - 5, 10, 20 ml Flac. 0,9% - 400ml; Flac. 10% - 200, 400 ml
4.	Kali Chloridum	Amp. 4% - 50 ml; Solutio 10% ad usum internum
5.	Calcii Chloridum	Amp. 10% - 5, 10 ml; Solutio 5% - 10% ad usum internum
6.	Calcii Cluconas	Pulv.; Tab. 0,5, 0,25; Amp. 10% - 10 ml
7.	Magnesii Culfas	Pulv.; Amp. 25%, 20% - 5, 10, 20 ml
8.	Glucosum	Pulv.; tab. 0,5; Flac. 5% - 400ml;

		Amp. 40% - 10, 20 ml;
		Amp. 25% - 20 ml
9.	Albuminum Cumanum	Amp. 5% - 50, 100, 250 ml
10.	Polyglucinum	Flac. 400 ml
11.	Neohaemodesum	Flac. 100, 200, 400 ml
12.	Lipofundin	Flac. emulsum 20% 400 ml

Anti-inflammatory agents

The anti-inflammatory agents are divided in two groups:

- 1) **Nonsteroid anti-inflammatory agents;**
- 2) **Steroid anti-inflammatory agents.**

The inflammatory response is a highly complex process which involves a number of cell types of the reticulo-endothelial system and a number of chemical mediators, including prostaglandins, leukotrienes, kinins, and biogenic amines. The arachidonic acid metabolism is inflammatory cascade leading to the synthesis of the proinflammatory prostaglandins and leukotrienes. Rheumatoid arthritis is the original condition for which antiinflammatory agents are used, and they remain a mainstay of therapy. Based on the concept that asthma is an inflammatory disease which leads to airway obstruction, inhaled glucocorticoids are the first-line treatment for moderate to severe asthma. Inhaled preparations are particularly effective when used to prevent recurrent attacks. Steroids are used in other collagen diseases, such as lupus erythematosus; in hypersensitivity or allergic states, such as nephrotic syndrome, ulcerative colitis, and Crohn's disease; in granulomatous disease, such as sarcoid; and in a wide range of dermatological and ophthalmological conditions. Steroids are valuable in the prevention and treatment of organ transplant rejection and in the improvement of muscle function in polymyositis. Corticosteroids are the mainstay of therapy for inflammatory demyelinating polyneuropathies. In Guillain-Barre syndrome glucocorticoids reduce the inflammatory attack and improve final outcome, while in chronic inflammatory demyelinating polyneuropathy glucocorticoids suppress the immune reaction but may not retard the progression of the disease. Glucocorticoids also

exert a facilitatory action on neuromuscular transmission which may contribute to their efficacy in certain neuromuscular disorders. The fact that acetylcholine receptor antibodies are responsible for the neuromuscular transmission defect in myasthenia gravis has provided rationale for exploiting the immunosuppressive effect of glucocorticoids.

Nonsteroidal anti-inflammatory drugs (nsaids)

Classification of non-steroid anti-inflammatory drugs is similar to classification of non-narcotic analgetics.

Salicylates

Acidum acetylsalicylicum (Aspirinum) was first isolated in 1829 by Leroux from willow bark, yielding a bitter glycoside called **salicin**, a white crystalline substance.

Pharmacokinetics: Acidum acetylsalicylicum has three therapeutic dose ranges: the low range (< 300 mg/d) is effective in reducing platelet aggregation; intermediate doses (300-2400 mg/d) have antipyretic and analgesic effects; and high doses (2400-4000 mg/d) are used for their anti-inflammatory effect. Acidum acetylsalicylicum is readily absorbed and is hydrolyzed in blood and tissues to acetate and salicylic acid. Salicylate is a reversible nonselective inhibitor of cyclooxygenase. Elimination of salicylate is first-order at low doses, with a half-life of 3-5 hours. At high (anti-inflammatory) doses, half-life increases to 15 hours or more and elimination becomes zero-order. Excretion is via the kidney. Oral absorption of salicylates is fairly rapid with appreciable blood levels appearing within 30 minutes and peaking at about 2 hours. Upon oral administration of the salicylates, a portion is rapidly absorbed from the stomach. Most of an orally ingested salicylate dose, however, is absorbed from the upper portion of the small intestine. Once absorbed, the salicylates are distributed throughout the body by a pH-dependent passive diffusion process. Most of the salicylates bind avidly to serum proteins. Biotransformation of salicylates occurs in the microsomal drug-metabolizing system, and the following metabolic products are seen in the urine: salicyluric acid (75%), phenolic glucuronide (10%), acyl glucuronide (5%), and free salicylic acid (10%).

Pharmacologic effects: Cyclooxygenase, the enzyme which converts arachidonic acid into the endoperoxide precursors of prostaglandin, has at least two different isoforms: COX-1 and COX-2. COX-1 is primarily expressed in noninflammatory cells, whereas COX-2 is expressed in activated lymphocytes, polyriiorphonuclear cells, and other inflammatory cells. Acidum acetylsalicylicum and the older nonselective NSAIDs inhibit both cyclooxygenase isoforms and thereby decrease prostaglandin and thromboxane synthesis throughout the body. Prostaglandins necessary for normal cell function are depleted, as well as prostaglandins involved in inflammation. The COX-2-selective inhibitors should have less effect upon the prostaglandins involved in normal cell function, particularly those in the gastrointestinal tract. The irreversible action of acidum acetylsalicylicum results in a longer duration of its antiplatelet effect. Acidum acethysalicylicum is rapidly effective in febrile patients, yet has little effect on normal body temperature, suggesting that prostaglandins have little influence on normal homeostatic mechanisms for body temperature. **The antipyretic action** is centrally mediated; the the CNS action is thought to be due to inhibited PGE₂ synthesis from the hypothalamus in response to an endogenous pyrogen. Salicylates and NSAIDs in general are **anti-inflammatory** due to the inhibition of prostaglandin synthesis. The primary clinical application is in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. **The analgesia** is usually effective for low-to-moderate intensity pain. Relief of pain occurs through both peripheral and central mechanisms. Peripherally, the salicylates inhibit the synthesis of prostaglandins in inflamed tissues, thus preventing the sensitization of pain receptors to both mechanical and chemical stimuli. Centrally, the analgesic site exists in close proximity to the antipyretic region in the hypothalamus. The analgesia produced by the salicylates is not associated with mental alterations, such as hypnosis or changes in sensation other than pain. Salicylates stimulate respiration directly and indirectly; oxygen consumption and carbon dioxide production are increased, particularly in skeletal muscle. This effect appears to be mediated by a salicylate-induced uncoupling of oxidative phosphorylation. The increased carbon dioxide

production stimulates respiration, but this is characterized by deep respirations rather than an increase in respiratory rate. High doses result in medullary stimulation, leading to hyperventilation and a respiratory alkalosis. Compensation rapidly occurs because the kidney is able to increase the excretion of bicarbonate, producing a compensated respiratory alkalosis. Toxic doses or very prolonged salicylate administration can depress the medulla, resulting in an uncompensated respiratory acidosis. Since renal bicarbonate excretion is elevated and since the salicylates cause the accumulation of organic acids, a metabolic acidosis also results. Therapeutic doses of salicylates have no significant cardiovascular effect. Large doses may cause peripheral vasodilation due to a direct effect on smooth muscle. Toxic doses depress circulation directly and by central vasomotor paralysis. The prophylactic use of acidum salicylicum to reduce thromboembolic events in coronary and cerebral circulation has widened. Because it can acetylate and inactivate cyclooxygenase, aspirin has important effects on the delicate balance which exists between the initiation and the inhibition of platelet aggregation. Vascular injury and exposure to subendothelial structures result in activation of the platelet cyclooxygenase enzyme system, leading to the production of TXA_2 , via thromboxane synthetase. TXA_2 is capable of inducing platelet aggregation. Concurrently opposing this physiologic process is the cyclooxygenase and prostacyclin synthetase enzyme system of the vascular endothelium. Instead of thromboxane synthetase, vascular endothelial cells contain a prostacyclin synthetase, which converts the cyclooxygenase products PGC_2 and PGH_2 to PGI_2 , a potent inhibitor of platelet clumping. It is thought that acidum acetylsalicylicum in appropriate doses can preferentially inhibit the platelet cyclooxygenase system, blocking the formation of TXA_2 and thereby suppressing platelet clumping. By inhibiting initial platelet aggregation to subendothelial structures, acidum acetylsalicylicum also prevents the secondary release of adenosine diphosphate (ADP) from platelet granules, a process which normally occurs when platelets clump. ADP release ordinarily brings about additional waves of platelet aggregation, leading to thrombus formation.

Therapeutic uses: The salicylates are used in restricted situations for the

symptomatic relief of fever. Because of an increased incidence of Reye's syndrome in children who previously have been given acidum acetylsalicylicum for the relief of viral fevers, it is now recommended that a child with any fever be given paracetamol instead, if medication is required. The salicylates are useful as analgesics for certain categories of pain (e.g. headache, arthritis, and dysmenorrhea). The salicylates, by way of their anti-inflammatory action, provide relief of symptoms in acute rheumatic fever. The salicylates remain the standard drug in the therapy of rheumatoid arthritis. Clinicians recommend small daily doses of acidum acetylsalicylicum for prophylaxis of thromboembolism, stroke, or myocardial infarction, because of acidum acetylsalicylicum's antiplatelet activity.

Adverse effects: Salicylates can cause epigastric distress, nausea, and vomiting due to irritation of the gastric mucosal lining and stimulation of the chemoreceptor trigger zone (CTZ) in the CNS. Salicylates and NSAIDs in general, may cause a dose-related gastric ulceration, bleeding, exacerbation of peptic ulcer symptoms, and erosive gastritis. Salicylates can produce at least two forms of hepatic injury. One form is dose-dependent and usually occurs in patients with connective tissue disorders (elevated plasma transaminase levels). A second form of salicylate-induced hepatic injury is more severe and associated with the encephalopathy seen in Reye's syndrome. Salicylates can cause salt and water retention, increasing circulating plasma volume (about 20%) in patients taking large doses. In patients with congestive heart failure, impaired renal function, or hypovolemia, salicylates can further exacerbate renal dysfunction. Salicylates also affect uric acid secretion, but the effect is dose-dependent: Low doses may decrease urate excretion while large doses may induce uricosuria.

Derivative of aniline

Paracetamol is an effective analgesic and antipyretic agent, but it has no anti-inflammatory activity, for reasons that are not completely understood. Paracetamol appears to be an inhibitor of prostaglandin synthesis in the brain, thus explaining its analgesic and antipyretic activity, but it is much less effective than acidum acetylsalicylicum as an inhibitor of the peripherally located prostaglandin

biosynthetic enzyme system which plays such an important role in inflammation. Paracetamol exerts little or no pharmacologic effect on the cardiovascular, respiratory, or gastrointestinal systems, on acid-base regulation, or on platelet function.

Therapeutic uses: Paracetamol provides an effective alternative when acidum acetylsalicylicum is contraindicated (e.g. in patients with peptic ulcer or hemophilia) and when the anti-inflammatory action of acidum acetylsalicylicum is not required.

Adverse effects: Skin rash and drug fever (hyperpyrexia caused by an allergic reaction to the drug). Rare instances of blood dyscrasias. Renal tubular necrosis and renal failure. Hypoglycemic coma. An overdose of Paracetamol can result in severe hepatotoxicity, resulting in centrilobular hepatic necrosis. The toxic metabolite of Paracetamol appears to be inactivated in the liver via glutathione. When glutathione stores are consumed, the N-acetyl-p-benzoquinone metabolite binds covalently to cellular constituents, producing hepatocellular damage. Although clinical symptoms, such as nausea and vomiting, occur during the first 24 hours after toxic ingestion, signs of hepatic damage (e.g. enzyme abnormalities) may not occur for 2-6 days.

Derivatives of indolacetic acid

Indomethacinum is a potent NSAID with increased toxicity. It has high bioavailability and absorption. Maximal concentration is viewed in 1-2 h after administration. It is biotransformed in liver by glucuronisation, demethylation and separation of chlorbenzol radical. Excretion is occurred by bile and urine. It has prominent anti-inflammatory effect. It is antipyretic, analgesic effects are more than in acidum acetylsalicylicum and paracetamol. Drug has also antiplatelet, uricosuric effects.

Therapeutic uses: The major uses of indomethacinum are in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout. Because of its toxicity and side effects, it is not routinely used for analgesia or antipyresis.

Adverse effects: Gastrointestinal complaints include: anorexia, nausea, and

abdominal pain; ulcers, sometimes with perforations and hemorrhage; diarrhea, sometimes associated with ulcerative lesions of the lower gastrointestinal tract. CNS effects, which are the most frequently reported, including: severe frontal headache, dizziness and vertigo, mental confusion, severe depression, psychosis, hallucination, and suicide. Hematologic reactions, such as neutropenia, thrombocytopenia, and, rarely, aplastic anemia. Hypersensitivity reactions, such as rashes, itching, urticaria, and acute asthma.

Sulindacum is an anti-inflammatory, analgesic, and antipyretic drug with a relative strength of about half of Indomethacinum's potency. Sulindacum is a prodrug. Its sulfide metabolite is more than 500 times more potent (than sulindac) as an inhibitor of cyclooxygenase.

Therapeutic uses: Sulindacum is primarily used in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute gout.

Adverse effects: Sulindacum has a lower incidence of toxicity as compared to Indomethacinum. Despite initial claims, sulindac does not appear to be "renal-sparing" and should be used cautiously in patients with compromised renal function.

Derivatives of antranil acid.

Acidum mefenamicum are anti-inflammatory, analgesic, and antipyretic. Analgesic and antipyretic activity is more than in salicylates. It produces interferonum synthesis and inhibits protheasis more than other non-steroid anti-inflammatory drugs. The drug is absorbed and metabolized quickly (by oxidation and glucuronisation), excreted with urine.

Therapeutic uses: Acidum mefenamicum is primarily used as an analgesic in rheumatoid arthritis, soft-tissue injury, dysmenorrheal, virus infections.

Adverse effects: The most commonly effects involve the gastrointestinal system and include dyspepsia or general discomfort. Diarrhea, which may be severe and associated with steatorrhea or bowel inflammation, is also common. Hemolytic anemia is a serious side effect and may be of an autoimmune origin. Allergic reactions

Tolmetinum is a NSAID which is more potent than acidum acetylsalicylicum

but less potent than Indomethacinum. The major therapeutic indication for tolmetinum is the treatment of juvenile and adult rheumatoid arthritis, as well as osteoarthritis.

Acidum propionicum derivatives include: Ibuprofenum, Naproxenum, Ketoprofenum, and Flubiprofenum.

These agents offer significant advantages over acidum acetylsalicylicum in and Indomethacinum because they are better tolerated at anti-inflammatory doses. All of these compounds can induce gastrointestinal side effects or alter platelet function; some may alter leukocyte function and motility.

Ibuprofenumum is equal to acidum acetylsalicylicum in its anti-inflammatory effect, but it is a more effective analgesic than acidum acetylsalicylicum or paracetamolum. It has some antipyretic action. Ibuprofenumum has a half-life of about 2 hours, is relatively safe, and is the least expensive of the older, nonselective NSAIDs.

Therapeutic uses: Ibuprofenumum is used for the treatment of arthritis and osteoarthritis.

Adverse effects: gastrointestinal effects occur in about 5%-15% of patients, but the incidence of these events is less than with acidum acetylsalicylicum or Indomethacinum; allergic reactions

As an NSAID, **naproxenum** is used for the treatment of rheumatoid arthritis and osteoarthritis. Naproxenumum is noteworthy because of its longer half-lives (15-20 hours), which permit less frequent dosing.

Adverse effects. While the incidence of gastrointestinal and the CNS effects approximate those of naproxenumum is better tolerated. Less commonly seen are pruritus and dermatologic problems. Isolated cases of jaundice, renal dysfunction, angioneurotic edema, thrombocytopenia, and agranulocytosis have been reported. Naproxenum does cross the placenta and appears in the milk of lactating women at about 1 % of the maternal plasma level.

Ketoprofenum exhibits a profile similar to ibuprofenumum, but slightly longer half-lives are seen in elderly patients.

Adverse effects. Gastrointestinal effects (30%) are generally less severe than those seen with aspirin and may be reduced further by taking the drug with food, milk, or antacids. Renal function should be monitored in patients over 60 or with impaired renal function. Patients treated concurrently with ketoprofen and dexketoprofen can experience hepatotoxicity.

Flurbiprofen has a profile similar to ibuprofen, but its plasma half-life is about 6 hours.

Oxicams.

As an anti-inflammatory agent, **piroxicam** is equipotent to indomethacin, acetylsalicylic acid, and naproxen. Piroxicam may also inhibit activation of neutrophils, suggesting an additional mode of anti-inflammatory action. As with other cyclooxygenase inhibitors, piroxicam is both analgesic and antipyretic. Effects of piroxicam last 24 hours.

Therapeutic uses: Piroxicam is approved for the use in the treatment of rheumatoid arthritis and osteoarthritis, but it has also been used in ankylosing spondylitis, musculoskeletal disorders, dysmenorrhea, postoperative pain, and gout.

Adverse effects. Piroxicam is better tolerated than acetylsalicylic acid or indomethacin; however, approximately 20% of patients taking piroxicam report an adverse effect. Gastrointestinal side-effects are most common with an incidence of less than 1 % for peptic ulcer. Piroxicam may cause allergic reactions.

Meloxicam is a selective inhibitor of COX-2 and has fewer adverse effects. COX-2 inhibitors are primarily used in inflammatory disorders. Selected NSAIDs are also used to treat other conditions, including dysmenorrhea, headache, and patent ductus arteriosus in premature infants. Derivatives of phenylacetic acid

Diclofenac-sodium is a potent anti-inflammatory, antipyretic, and analgesic agent; it is a more potent inhibitor of cyclooxygenase than indomethacin or naproxen. Additionally, diclofenac-sodium appears to alter the release or uptake of fatty acids, reducing intracellular levels of arachidonic acid in leukocytes.

Therapeutic uses: Diclofenac-sodium is approved for use in the treatment of

rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It may also be useful for short-term treatment of acute musculoskeletal injury, tendinitis, bursitis, postoperative pain, and dysmenorrhea.

Adverse effects: Gastrointestinal symptoms (20%) are the most common; bleeding, ulceration, and perforation have been reported. Elevated hepatic transaminase levels.

Derivatives of sulphone acid

Nimesulidum is selective inhibitor of the COX-2 with antioxidant and low acidic properties, blocks phosphodiesterase, IV and metalloproteases, decrease content not only prostaglandines and also leucotrienes, TNF. It is used in rheumatoid, nonrheumatoid arthritis, allergic diseases.

Adverse effects. Nausea, vomiting, heartburn, gastralgia. Allergic reactions. Sometimes headache, dizziness, sleepiness.

Derivative of isonicotinic acid.

Amisonum has anti-inflammatory, analgetic, antipyretic, interferonogene, antioxidant effects.

Therapeutic uses: It is used in arthritis of different etiology, grippe, and other virus diseases.

Adverse effects. Bitter taste. Mucosal edema in mouth.

Coxibes.

Celecoxibum is selective inhibitor of the COX-2, has prominent analgetic and anti-inflammatory effects. **Rofecoxibum** and **Lumiracoxibum** have analgetic properties, are used for treatment of rheumatoid arthritis and osteoarthritis.

Adverse effects from gastrointestinal tract are rare but rofecoxibum causes adverse effects on cardiovascular system.

Ketorolac is notable as a drug used mainly as a systemic analgesic, not as an anti-inflammatory drug (though it has typical nonselective NSAID properties).

Steroid anti-inflammatory drugs.

Glucocorticoids are steroid anti-inflammatory drugs. Natural drug is Hydrocortisonum. Synthetic drugs are prednisolonum, methylprednisolonum,

betametasonum. Drugs with one fluoridum are dexametasonum and triamcinolonum. Drugs with two fluoridums are synaflanum and flumetasoni pivalas.

Mechanism of anti-inflammatory action:

1. Glucocorticoids inhibit phospholipase A₂ (the main mechanism), which controls synthesis of inflammatory mediators – prostaglandins, leucotriens, and trombocytes activating factor.
2. They decrease sensitivity of tissues receptors to inflammatory agents.
3. Block of capillary widening, leukocytes adhesion, migration (antiproliferative action). Drugs block activation of compliment system, blood coagulation, decrease ability of fibroblasts to proliferation and sclerotic process in general.
4. Glucocorticoids stabilize lisosome membranes and proteolytic activity of lisosome enzymes.

Therapeutic uses: Collagenosis, rheumatism, rheumatic arthritis, asthma, leucosis, mononucleosis, neurodermitis, skin diseases, allergic and autoimmune diseases, for shock prophylaxis and treatment.

	Drug	Drug forms
1.	Acidum Acetylsaliculicum	Tab. 0,25, 0,5; Tab. 0,075 – 0,325
2.	Analginum	Pulv.; Tab. 0,5; Amp. 25%, 50% - 1, 2ml
3.	Paracetamolum	Tab. 0,2; Ung. 5% - 20,0
4.	Acidum Mephenamicum	Tab. 0,25, 0,35, 0,5
5.	Ibuprophenum	Dragee 0,2 Tab. 0,2
6.	Diclofenac-natrium	Tab. 0,025

		Amp. 2,5% - 3ml
7.	Indomethacinum	Dragee, caps. 0,025; Tab. 0,01, 0,025, 0,1, 0,075; Ung. 10% - 40,0; Supp. rect. 0,05; Caps. 0,02
8.	Meloxicam	Tab. 0,0075, 0,015
9.	Amizonum	Tab. 0,25
10.	Celecoxibum	Caps. 0,1
11.	Nimesulidum	Tab. 0,1
12.	Pyroxicamum	Tab. 0,01; Caps. 0,02

13.	Hydrocortisonum	Flac. susp. 2,5% - 5ml; Ung. 1%, 2,5% - 10
14.	Prednisolonum	Tab. 0,001, 0,005; Amp. 3% - 1ml; Ung. 0,5% - 5; Flac. 0,3% 5ml
15.	Triamcinolonum	Tab. 0,001, 0,004; Ung. 0,1% - 15
16.	Dexamethasonum	Tab. 0,0005; Flac. 0,4% - 5ml; 0,1% - 5ml; Amp. 0,4% - 1ml

Immunopharmacology.

The primary features of cell-mediated and humoral immunity are:

1. B cells: Lymphoid cells derived from the bone marrow which mediate humoral (serologic) immunity through the formation of antibodies.

2. T cells: Lymphoid cells derived from the thymus which mediate cellular immunity and can modify serologic immunity. The main subclasses of T cells are CD4 (helper) cells and CD8 (suppressor) cells.

3. Antigen-presenting cells (APCs): Dendritic and Langerhans cells, macrophages, and B lymphocytes involved in the processing of antigens into cell-surface forms recognizable by lymphoid cells.

4. Clusters of differentiation (CDs): Specific cell surface constituents (characterized by monoclonal antibodies) identified by number (CD1, CD2, etc).

5. Major histocompatibility complex (MHC): Cell surface molecules which bind antigen fragments and, when bound to antigen fragments, are recognized by helper T cells. The MHC class I molecules are expressed by all cells, whereas MHC class II molecules are expressed by antigen-presenting cells.

6. Cytokines: Polypeptide modulators of cellular functions include interferons, interleukins, and growth stimulating factors.

7. Lymphokine: A cytokine which is capable of modulating lymphoid cell functions.

8. Immunophilins: Members of a highly conserved family of cytoplasmic proteins which bind to the immunosuppressants cyclosporine, tacrolimus, and sirolimus and assist these drugs in inhibiting T and B cell function. Cyclophilin binds cyclosporine, whereas FK-binding protein (FKBP) binds tacrolimus and sirolimus.

Immunopharmacology includes drugs which can suppress, modulate, or stimulate immune functions. It also includes antibodies which have been developed for use in immune disorders. The drugs available comprise a wide variety of chemical and pharmacologic types. The innate immune system initiates the defense against pathogens and antigenic insult. It involves the concerted actions of complement components, lysozyme, macrophages, and neutrophils. If the innate response is inadequate, the adaptive immune response is mobilized.

Drug influence on immune system are divided into:

1. Antiallergic drugs.

2. Immunotropic drugs.

2.1. Immunosuppressants (Immunodepressants).

2.2. Immunoregulators (Immunomodulators)

Antiallergic drugs.

Mechanisms of drug allergy. Immunologic reactions to drugs can fall into any of the four categories of hypersensitivity reactions.

They are classified into two groups:

I. Antiallergic drugs in immediate type of allergy (may be caused penicillinum etc.).

1.1. The drugs block allergy mediatory release from-smooth cells, eosinophils, slow down cytochemic cascade allergic process development.

1.1.1. Glucocorticoids-Hydrocortison acetate, Prednisolonum, Dexamethazonum, Methylprednisolonum, Triamcinolonum, Beclomethasoni dipropionas etc.

1.1.2. Xantines-Euphyllinum, Theophyllum.

1.1.3 Membranes stabilizers-cromolyn-sodium, ketotifenum etc.

1.1.4. H₁ receptors blockers-antihistaminic drugs-Dimedrolum, Diprazinum, Lorantadinum.

1.1.5. Desensibilizators-Histaglolulins.

1.1.6. Complement system inhibitors-heparinum, acidum aminocaproicum.

II. Antiallergic drugs in slowing allergy (may be caused by methyldopa, etc).

1. Nonsteroids anti-inflammatory drugs.

2. Immunodepressants.

H₁-Receptor Antagonists.

The H₁-antagonists are classified as either first-, second-, third-generation compounds. The most common use of the H₁ receptor antagonists is for the relief of allergic reactions such as rhinitis and urticaria. These compounds are also used to prevent motion sickness, to treat vestibular disturbances such as Meniere's syndrome, and as over-the-counter sleep aids. The H₁-receptor antagonists for the most part are substituted ethylamine compounds. In comparison with histamine the H₁-antagonists contain no imidazole ring and have substituents on the side chain amino group.

Second-generation antihistamines have lipophilicity and ionization profiles which make them less able to cross the blood-brain barrier; thus they produce dramatically less sedation than do the first-generation drugs. Third generation drugs are the metabolites of second-generation drugs.

First generation are **Dimedrolum, Diprazinum, Suprasinum, Diazolinum, Tavegilum, Phencarolum, Peritolum, Meclizinum.**

Second generation are **Loratadinum, Terfenadinum, Cetirizinum, Astemizolum.**

Third generation include **Desloratadinum (Erius), Texofenadinum (Telfastum).**

First-generation antihistamines are well absorbed after oral administration, with peak blood levels occurring within 1 to 2 hours; the therapeutic effect usually lasts 4 to 6 hours, although some drugs are much longer acting. These antagonists are generally metabolized in the liver through hydroxylation. The metabolites and a small amount of parent compound are excreted in the urine.

The second-generation H₁-receptor antagonists are also rapidly absorbed, with peak plasma concentrations being reached within 1 to 3 hours. Their duration of action generally varies between 4 and 24 hours. Loratadinum (Claritinum) and its active metabolite, desloratadine (Erius Clarinex), undergoes extensive first-pass metabolism and is converted by CYP3A4 isozymes to an active metabolite. A number of drug interactions result from the ability of various compounds to induce, inhibit, or compete for metabolism by this cytochrome P450 system. In contrast, cetirizinum (Zyrtec) and fexofenadine (Telfast Allegra) undergo little hepatic metabolism and are eliminated mainly as unchanged compounds in the urine and feces, respectively.

The reduction in therapeutic effectiveness which can occur when antihistamines are given for long periods is probably related to an induction of hepatic drug-metabolizing enzymes. Children tend to eliminate antihistamines more rapidly than adults, while individuals with hepatic impairment may eliminate them more slowly.

Mechanism of action: At therapeutic doses, the first- and second-generation antihistamines are equilibrium-competitive inhibitors of H₁-receptor-mediated responses. Certain second-generation drugs are noncompetitive inhibitors at high

concentrations. Both first- and second-generation compounds have negligible abilities to block the H₂-, H₃-, or H₄-receptors. The therapeutic effectiveness of these drugs arises from their capacity to block histamine-mediated vasoconstriction, microvascular permeability enhancement, and sensory nerve terminal stimulation. H₁-antagonists generally produce sedation through an effect on the CNS; however, excitation can occur when toxic dosages are ingested. Many of these drugs have effects which are not mediated by H₁-receptors. The antimuscarinic activity of several first-generation H₁-blockers may account for their effectiveness in combating motion sickness and their limited ability to suppress parkinsonian symptoms. The phenothiazines have some capacity to block α -adrenoceptors, where as cyproheptadine (Periactin) is an antagonist at serotonin receptors. Many second-generation antihistamines also have been found to inhibit the non-histamine-mediated release of various inflammatory substances; this may account for some of their effectiveness in allergic conditions.

Therapeutic uses: The H₁-receptor blocking drugs find their greatest use in the symptomatic treatment of allergic conditions. The second-generation antihistamines and the first-generation alkylamines are most frequently used to treat allergic rhinitis. Allergic conjunctivitis and the acute form of urticaria are also effectively treated with antihistamines. The allergic responses seen in susceptible individuals after intradermal injections of allergens (e.g. skin testing) can be prevented for several hours by prior administration of H₁ antagonists. However, the H₁ antagonists are not drugs of choice in acute anaphylactic emergencies or the viral-caused common cold. Although the antihistamines are not useful as primary agents in the treatment of asthma, a number of studies have shown which the second-generation compounds are effective as adjunctive therapies in asthmatic patients with concomitant rhinitis, urticaria, or dermatitis. Cetirizine has been used to prevent the progression from atopic dermatitis to asthma in young children. Another important use of H₁-antagonists is in the treatment of motion sickness. Many H₁-receptor blocking drugs have sedative properties, and some have been used in over-the-counter sleep aids. Cromolyn sodium and nedocromilum sodium are used as pulmonary inhalants in the treatment of asthma.

Nasal (Nasalcromum) ophthalmic (Opticromum) preparations of cromolyn sodium can be used to reduce the symptoms of allergic rhinitis and conjunctivitis. Ketotifen blocks H_1 -receptors and the release of histamine. Drug is used for bronchial asthma prophylaxis.

Adverse effects. Sedation is the most frequent adverse reaction to the first-generation antihistamines. An additive effect on alertness and motor skills will result if alcohol or another depressant is taken with these drugs. Antimuscarinic effects caused by these drugs include dry mouth and respiratory passages, urinary retention, and dysuria. Nausea, vomiting, constipation or diarrhea, dizziness, insomnia, nervousness, and fatigue also have been reported. Drug allergy, especially after topical application, is fairly common. Tolerance to certain antihistamines may develop after prolonged administration. Teratogenic effects of the piperazine antihistamines have been shown in animal studies. Epidemiological studies have not shown such an association in humans. The effects of toxic doses of first-generation antihistamines, similar to those seen following atropine administration, include excitement, hallucinations, dry mouth, dilated pupils, flushing, convulsions, urinary retention, psinus tachycardia, coma, and death.

The second-generation H_1 antagonists are often referred to as nonsedating antihistamines; however, doses above the usual therapeutic level can cause sleepiness in certain individuals. A more serious adverse effect of some earlier second-generation antihistamines is cardiotoxicity. Terfenadinum and astemizolum in rare cases to induce a potentially fatal ventricular arrhythmia, torsades de pointes. These drugs block the cardiac K^+ channels responsible for the repolarizing current (I_{Kr}) of the action potential and therefore prolong the QT interval. Arrhythmias result when these drugs accumulate to toxic levels, such as when their metabolism is impaired, as in liver disease or following coadministration of drugs which inhibit the CYP3A family of enzymes. Fexofenadinum, the active antihistaminic metabolite of terfenadine, does not produce torsades de pointes.

1. Immunosuppressants are divided into:

1.1 Cytostatics block synthesis of the RNA, depress antibodies formation

defenced from T-lymphocytes innated by antigen. They block lymphokins production and release. They have cytotoxic effects in high doses. Such cytostatic as azathioprinum, cyclosporinum, cyclophosphamidum are used as immunodepressants.

1.2 Glucocorticoids immunodepressive effect is connected with anti-inflammatory action with blocking of cytokins production, NO synthesis, phospholipase A₂ activity, stimulating of interleukin-10 production etc. Such glucocorticoids as hydrocortisoni acetat, prednisolonum, methylprednisolonum, dexamethasonum, triamcinalonum, beclomethasonidi propionas etc. are used as immunodepressants.

1.3. The drugs of different chemical groups.

1.3.1. Aminochinolines derivatives – chingaminum, plaquenilum block nucleinic acid synthesis.

1.3.2. Aurum drugs crysunolum etc depress humoral immunitetum.

1.3.3. Acidum micophenolicum derivatives – celcetum etc have prominent cytotoxic action.

1.3.4. Immunoglobulines and antibodies.

Corticosteroids.

Mechanism of action: Glucocorticoids act at multiple cellular sites, leading to broad effects on inflammatory and immune processes. At the biochemical level, their actions on gene expression lead to decreases in the synthesis of prostaglandins, leukotrienes, cytokines, and other signaling molecules which participate in immune responses (e.g. platelet activating factor). At the cellular level, the glucocorticoids inhibit the proliferation of T lymphocytes (suppressing cellular immunity) and, to a lesser degree, dampen humoral immunity. At doses used for immunosuppression, the glucocorticoids are cytotoxic to certain subsets of T cells. Continuous therapy lowers IgG levels by increasing catabolism of this class of immunoglobulins.

Therapeutic uses: Glucocorticoids are used alone or in combination with other agents in a wide variety of medical conditions involving an undesirable immunologic reaction. Their ability to induce apoptosis in immune cells makes them

useful for treatment of several types of cancer. Corticosteroids are also used to suppress immunologic reactions in patients who undergo organ transplantation.

Cyclosporinum, Tacrolimus:

Mechanism of action: These peptide antibiotics interfere with T cell function by binding to **immunophyllins**, small cytoplasmic proteins which play critical roles in T cell responses to TCR activation and to cytokines. **Cyclosporinum** binds to cyclophilin and **tacrolimus** binds to FK-binding protein (FKBP), both complexes inhibiting **calcineurin**, a cytoplasmic phosphatase. Calcineurin regulates the ability of the nuclear factor of activated T cells (NF-AT) to translocate to the nucleus and increase the production of cytokines. Cyclophilin and tacrolimus both inhibit the production of cytokines which normally occurs in response to TCR activation.

Therapeutic uses and pharmacokinetics. Use of these immunosuppressants is a major factor in the success of solid organ transplantation. Cyclosporinum is used in solid organ transplantation and in graft-versus-host syndrome in bone marrow transplants. Tacrolimus is used in liver and kidney transplant recipients and may be effective as rescue therapy in patients who fail standard therapy. The agents, particularly cyclosporine, may also be effective in immune diseases, including rheumatoid arthritis, uveitis, psoriasis, asthma, and type 1 diabetes. All three agents can be used orally. However, since cyclosporine exhibits erratic bioavailability, serum levels should be monitored. The drug undergoes slow hepatic metabolism by the cytochrome P450 system and has a long half-life. Its metabolism is affected by a host of drugs. Cyclosporinum and tacrolimus have similar toxicity profiles.

The most frequent **adverse effects** are renal dysfunction, hypertension, and neurotoxicity. They may also cause hyperglycemia, hyperlipidemia, and cholelithiasis.

Celcetum (Mycophenolate Mofetil):

Mechanism of action: This drug is rapidly converted into mycophenolic acid, which inhibits inosine monophosphate dehydrogenase, an enzyme in the de novo pathway of purine synthesis. This action suppresses both B and T lymphocyte activation.

Therapeutic use: The drug has been used successfully as a sole agent in kidney, liver, and heart transplants. In renal transplants, its use with low-dose cyclosporine has reduced cyclosporine-induced nephrotoxicity.

Apart from its gastrointestinal side effects, the drug appears to be quite safe.

Azathioprinum:

Mechanism of action: This prodrug is transformed to the antimetabolite mercaptopurinum, which upon further metabolic conversion inhibits enzymes involved in purine metabolism. Azathioprinum is cytotoxic in the early phase of lymphoid cell proliferation and has a greater effect on the activity of T cells than B cells.

Therapeutic use: Azathioprinum is used in autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis) and for immunosuppression in renal homografts. The drug has minimal effects on established graft rejections.

The major toxic effect is bone marrow suppression, but gastrointestinal irritation, skin rashes, and liver dysfunction also occur. The use of azathioprinum is associated with an increased incidence of cancer. The active metabolite of azathioprinum, mercaptopurinum, is metabolized by xanthine oxidase, and toxic effects may be increased by allopurinol given for hyperuricemia.

Cyclophosphamidum and other cytostatics are used in complex pharmacotherapy.

Mechanism of action: This orally active prodrug is transformed by liver enzymes to an alkylating agent which is cytotoxic to proliferating lymphoid cells. The drug has a greater effect on B cells than T lymphocytes and will inhibit an established immune response. Other cytotoxic drugs which similarly suppress proliferating lymphoid cells – and are sometimes used as immunosuppressants – include **mercaptopurinum, cytarabinum, dactinomycinum, methotrexatum, vincristinum etc.**

Therapeutic use: Cyclophosphamidum is effective in autoimmune diseases (including hemolytic anemia), antibody-induced red cell aplasia, bone marrow transplants, and possibly other organ transplant procedures. Cyclophosphamidum does not prevent the graft-versus-host reaction in bone marrow transplantation.

Large doses of the drug (usually needed for immunosuppression) cause pancytopenia, gastrointestinal distress, hemorrhagic cystitis, and alopecia. Cyclophosphamidum (and other alkylating agents) may cause sterility.

New Immunosuppressants are used in many countries. **Etanerceptum:** This chimeric protein is a recombinant form of the human TNF receptor. The agent binds TNF- α , a proinflammatory cytokine, and thereby decrease formation of interleukins and adhesion molecules involved in leukocyte activation. Etanercept is used in rheumatoid arthritis and is being investigated in other inflammatory diseases. Injection site reactions and hypersensitivity may occur. **Leflunomidum:** This drug inhibits dihydroorotic acid dehydrogenase, an enzyme involved in ribonucleotide synthesis. Leflunomide arrests lymphocytes in the G₁ phase of the cell cycle. Leflunomide is used in rheumatoid arthritis. The drug causes alopecia, rash, and diarrhea. **Thalidomidum:** This sedative drug, notorious for its teratogenic effects, has immunosuppressant actions which appear to be due to suppression of TNF production. Thalidomidum is used for some forms of leprosy reactions, for immunologic diseases (e.g. systemic lupus) and as an anticancer drug. It is also effective in treating aphthous ulcers and the wasting syndrome in AIDS patients.

Lymphocyte Immune Globulin is used as supplementary drug.

Mechanism of action: Lymphocyte immune globulin (LIG), also known as antithymocyte globulin (ATG), is usually produced in horses by immunization against human thymus cells. Lymphocyte immune globulin binds to T cells involved in antigen recognition and initiates their destruction by serum complement. Lymphocyte immune globulin selectively blocks cellular immunity rather than antibody formation, which accounts for its ability to suppress organ graft rejection.

Therapeutic use: Lymphocyte immune globulin is used prior to bone marrow transplantation to prevent the graft-versus-host (GVH) reaction. It is also used in combination with cyclosporine or cytotoxic drugs (or both) for maintenance following bone marrow, heart, and renal transplantations. Lymphocyte immune globulin has induced remissions in patients with aplastic anemia. Since serologic immunity may remain intact, injection of lymphocyte immune globulin may cause

hypersensitivity reactions, including serum sickness and anaphylaxis. Pain and erythema occur at injection sites, and lymphoma has been noted as a late complication.

Monoclonal Antibodies (Muromonab, Daclizumab, Infliximab): Monoclonal antibodies (MAbs) have the potential advantage of high specificity, since they can be developed for interaction with a single molecule. "Humanization" of murine monoclonal antibodies has reduced the likelihood of formation of neutralizing antibodies and of immune reactions.

IMMUNOMODULATING AGENTS

Agents which act as stimulators of immune responses represent a new area in immunopharmacology with the potential for important therapeutic uses, including the treatment of immune deficiency diseases, chronic infectious diseases, and cancer.

The main groups of immunomodulating agents include

1. Thymus gland drugs - Thymalinum, Tactivinum, Thumosimum etc. Thynialinum and Factivinum are the complex of polypeptides fractions of thymus gland of horned cattle. They are drugs of first generation. They stimulate immune reactions, restore Tlympocytes quantity and function, correlation of T- and B-lymphocytes, their subpopulations and increase native killers activity, intensify phagocytosis and lymphokines production. They are used in complex therapy of immune deficiency diseases trophic ulcers, after prominent and chemotherapy etc. Thymosinum is protein hormone from the thymus gland which stimulates the maturation of pre T-cells and promotes the formation of T-cells from ordinary lymphoid stem cells. Thymosin-containing preparations have been used in Di-George's syndrome (thymic aplasia).

2. Other immunopeptide drugs - Myelopidum (consists of 6 myeloptides from marrow cells), immunophanum (synthetic hexapeptidum) which are used in immune deficiency diseases: Glatiramer acetate synthetic neuropeptides similar to myelinum to treat disseminated sclerosis.

3. Interferons.

3.1 Native interferons from donor blood leucytes- interferonum-alpha, interferonum-beta, interferonum-N1

3.2 Recombinant are obtained by genno- engeniring method- interferonum alpha-2 α (Roferonum),interferonum alpha- 2- β (Laferonum, intronumt),interferonum beta-1- α (Rebifum), interferonum-beta-1 β (Betaferonum), Pegiferonum 2- σ b (Pegintronum) etc.

4. Interleukins (Roncoleukinum).

5. Drugs microlial origin – BCG (Bacille Culmette Guerin). BCG is used for immunization against tuberculosis immunostimulant in cancer diseases.

Lactoacillus-lactobacterium-probiotics- Chylack-forte; biphidobacterias-bifidobacterinum, combinations of microorganisms-Biosporinum, Bipicolum, Linex.

6. Active components of plants - Extraktum Echinaceae fluidum, Extractum Rodiolas fluidum etc.

7. Synthetic drugs - Amixinum, Cydosporinum, Laevamisolum, Methyluracylum.Polyoxydonium promote interferonum synthesis, some of themactivate T-lymphocytes synthesis.

8. Enzymes for systhemic therapy: Wobenzymum, Flogenzymum which form complexes with algogenic compounds, albuminum aminoacids increase antitoxic function of liver, normalize lymphocytes function.

9. Myeloid colony-stimulating factors: Filgrastimum, Molgramostimum, Sargamostimum, Lenograstimum are cytokins, or growth factors, which support the survival clonal expansion and differentiation of hemopoietic cells. They are used in prominent, chimiotherapy.

10. Embrional tissues drugs- Propesus, Erbisolum activate macrophage, T and B lymphocytes.

11. Vitamins Tocoferoli acetas, Acidum nicotinicum, Retinoli acetas, Acidum ascorbinicum.

12. Immunoglobulines which contain a distribution of all subclasses with antibody titers for most major bacterial,viral , fungal pathogens-immunoglobulinum human contra herpes virus, immunoglobulinum human contra virus hepatitis B.

Romoleukinum: Romoleukinum is recombinant interleukin-2 (IL-2), an endogenous lymphokine which promotes the production of cytotoxic T cells and activates natural killer cells. Romoleukinum is indicated for the adjunctive treatment of renal cell carcinoma. It is investigational for possible efficacy in restoring immune function in AIDS and other immune deficiency disorders.

Interferons: Interferon- α -2a (Laberonum) inhibits cell proliferation and is used in hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, Kaposi's sarcoma, and hepatitis B and C. **Interferon- β -1b** has some beneficial effects in relapsing multiple sclerosis. **Interferon- γ -1b** has greater immune-enhancing actions than the other interferons and appears to act by increasing the synthesis of TNF. The recombinant form is used to decrease the incidence and severity of infections in patients with chronic granulomatous disease.

№	Drug	Drug forms
1.	Dimedrolum	Pulv.; Tab. 0,005, 0,01, 0,02, 0,03, 0,05; Supp. 0,005, 0,01; Amp. 1% - 1ml; Guttas 0,2–0,5%
2.	Diprasinum	Pulv.; Tab. 0,025; Dragee 0,025, 0,05; Amp. 2,5% - 2ml
3.	Diazolinum	Pulv.; Dragee 0,05-0,1
4.	Suprastinum	Tab. 0,025; Amp. 2% - 1ml
5.	Phencarolum	Tab. 0,025; Amp. 2% - 1ml

6.	Tavegilum	Tab. 0,001; Amp. 0,1% - 2ml
7.	Loratadinum	Tab. 0,01; Sirupus 60ml, 100ml, 120ml
8.	Fexofenadinum	Tab. 0,12, 0,18
9.	Cromolyn Sodium (Intalum)	Caps. 0,02 №30
10.	Ketotifenium	Tab., caps. 0,001; Sirupus 0,02%
11.	Tactivinum	Flac. 0,01% - 1ml
12.	Thymalinum	Flac. 0,01

TREATMENT OF POISONING

Toxicology is the study of poisons, including their actions, adverse effects, and treatment of the conditions which they produce. These poisons include household, environmental, industrial, or pharmacologic substances.

Antidotes have been developed for some poisons. These act either by preventing absorption or by inactivating or antagonizing the actions of the poisons.

General approach to the treatment of acute poisoning include:

1. Reduce absorption and enhance removal of poisoning.
2. Administer antidote to render harmless.
3. Provide emergency management.

1. For reduction absorption and enhancement removal of poison:

1.1. Irritation eyes, skin with physiological solutions, in some cases with special antidotes (e.g. Kalii permanganas is neutralized by solution of acidum ascorbinicum);

1.2. Emesis induce with apomorphini hydrochloridum, parenterally, solutio Ammonii caustici per os or mechanically;

1.3 Performance gastric lavage with Kalii permanganas solution, physiological solution, in the case of metals intoxication with unithiolum; of acids intoxication with water or magnesi oxydum etc.;

1.4 Administration activated charcoal to bird poison and other adsorbents

(Enterogelum etc.);

1.5 Administration adstringents: milk, egg-white, mucilages;

1.6 Consider forced diuresis urine (Furosemidum or Mannitum with solutio Natrii chloridi isotonica);

1.7 **Cathartics** are used to hasten the removal of a toxic substance and are useful for ingestion of hydrocarbons and enteric-coated tablets. **Magnesii sulfas** is a frequently used cathartic;

1.8 Hemodialysis or charcoal hemoperfusion, hemosorbition lymphodyalysis, lymphosorbition, peritoneal dialysis may be appropriate for rapid elimination.

Chelating agents as antidotes.

Chelators are organic compounds with two or more electronegative groups which can form stable covalent-coordinate bonds with cationic metal atoms. These stable complexes can often be excreted readily, thus reducing the toxicity of the metal.

The most useful chelators for clinical purposes are mecaptides – unithiolum, dimercaprolum (BAL), succimer; other chelators penicillaminum, natrii edetas (EDTA), tetacinum-calcium and deferoxaminum. Variations among these agents in their affinities for specific metals govern their clinical applications.

Unithiolum (2, 3 - dimercaptopropan-sulphonate natrii; was created by A.I. Cherkes); **dimercaprolum** (2, 3 - dimercaptopropanol; British antilewisite) are bidentate chelators, i.e. they form two bonds with the metal ion, preventing the metal's binding to tissue proteins and permitting its rapid excretion with urine.

Therapeutic use: Unithiolum and Dimercaprolum are used in acute arsenic, mercury, other heavy metals poisoning, cardiac glycosides poisoning, – and for lead poisoning when administered with natrii edetas. Unithiolum is water soluble. Dimercaprolum is an oily liquid which must be given parenterally. They are used in hepatocerebral dystrophy and alcoholism treatment.

Adverse effects: Unithiolum is less toxic, it may cause nausea, tachycardia, dizziness, paleness. Dimercaprolum causes a high incidence of adverse effects, possibly because it is very lipophilic and readily enters cells. Its adverse effects includes transient hypertension, tachycardia, headache, nausea and vomiting, paresthesias, and fever

(especially in children). It may cause pain and hematomas at the injection site. Long-term use is associated with thrombocytopenia and increased prothrombin time.

Succimerum (2,3-dimercaptosuccinic acid) is a water-soluble bidentate congener of dimercaprolum with oral bioavailability.

Therapeutic use: Succimerum is used for the oral treatment of lead toxicity in children and adults, and it is as effective as parenteral EDTA in reducing blood lead concentration. Succimer is effective in arsenic and mercury poisoning, if given within a few hours of exposure.

Adverse effects: While succimerum appears to be less toxic than dimercaprolum, gastrointestinal distress, CNS effects, skin rash, and elevation of liver enzymes may occur.

Thanks to sulfhydryl groups Natrii thiosulfas and acetylcysteinum may be used in the cases of metal intoxication.

Penicillaminum: Penicillaminum, a derivative of penicillin, is another bidentate chelator, forming two bonds with the metal ion.

Therapeutic use: The major uses of penicillaminum are in the treatment of copper poisoning and of Wilson's disease. It is sometimes used as adjunctive therapy in gold, arsenic, and lead intoxication and in rheumatoid arthritis. The agent is water-soluble, well absorbed from the gastrointestinal tract, and excreted unchanged.

Adverse effects are common and may be severe. They include nephrotoxicity with proteinuria, pancytopenia, and autoimmune dysfunction, including lupus erythematosus and hemolytic anemia.

Natrii edetas (EDTA) is a very efficient polydentate chelator of many divalent and trivalent cations (including calcium).

Clinical use: The primary use of natrii EDTA is in the treatment of metals, including lead poisoning, cardiac glycosides poisoning. Because the agent is very polar, it is given parenterally and it does not enter cells. To prevent dangerous hypercalcemia, EDTA is usually given in calcosi, in sclerodermy, arthritis etc.

Adverse effects: The most important adverse effect of the agent is nephrotoxicity, including renal tubular necrosis. This risk can be reduced by adequate hydration and restricting treatment with EDTA to 5 days or less. Electrocardiographic changes may

occur at high doses.

Tetacinum – calcium (calcium EDTA) chelates with metal ions which is more stable than it lead, thorium, cadmium, mercury, cobalt, uranium, yttrium, caesium etc.

Therapeutic use: acute and chronic intoxication with heavy and rare metals.

Adverse effects: diarrhea, toxic nephrosis, hemogloin, iron, vitamins contents diminution.

Pentacinum (calcium trisodium salt EDTA) is used in acute and chronic heavy and radioactive metal intoxications. **Adverse effects** include dizziness, headache, pains in extremities and thorax.

Ferrocinum is antidote in radioisotopes of uranium, radium, cesium intoxication; trimethacinum is antidote in radioactive metals (uranium etc) intoxication.

Antidotes of methhemoglobine forming poisons. Cyanide ions form complexes with ferric ions of the cytochrome oxidase system interfering with electron transfer in the cytochrome a – a₃ complex. This leads to a blockage in oxygen transfer to tissues and causes a cytotoxic hypoxia. **Natrii nitras** is administered intravenously. Methhemoglobin is formed which has a greater affinity for cyanide ion than does cytochrome a – a₃. The cyanide – cytochrome complex, therefore dissociated and normal oxidative metabolism resumes. **Methylenum coeruleum** may also transform hemoglobin in methhemoglobin interacting with cyanides. Other specific antidotes acting poisons biotransformation **natrii thiosulfas** forms with cyanides non toxic rodant compounds. **Spiritus aethylicus** protect methylenic aldehyde formation in spiritus methylenic intoxication.

Deferoxaminum: Deferoxaminum is a polydentate bacterial product which has an extremely high and selective affinity for iron and a much lower affinity for aluminum. Fortunately, the drug competes poorly for heme iron in hemoglobin and cytochromes.

Therapeutic use: Deferoxaminum is used parenterally in the treatment of acute iron intoxication.

Adverse effects: Skin reactions (blushing, erythema, and urticaria) may occur. With long-term use neurotoxicity (e.g. retinal degeneration), hepatic and renal dysfunction, and severe coagulopathies have been reported. Rapid intravenous administration may cause histamine release and hypotensive shock.

Some specific antidotes for toxic drugs and chemicals

Protamini sulfas is antidotum of heparinum because ionically neutralizes heparinum. Vikasolum is antidotum to indirect anticoagulants (warfarinum etc) because stimulates coagulation factor synthesis.

Naloxoni hydrochloridum is antidote of narcotic analgetics because displaces drugs from receptors.

Glucosum is antidote of insulinum because reverses glucose depletion.

Dipiroxinum, Isonitrozinum are antidotes to organophosphates because reduct cholinesterase activity.

Flumazemylum is benzodiazepine compounds antidotum displaces drugs from receptors.

M – cholinoblockers (atropine sulfas, scopolamine hydrobromidum) are antidotes to M – cholinomimetics, anticholinesterase blocking drugs (proserinum, galanthamini hydrocarbonas) are antidotes to antidepolarazing myorelaxants and M – cholinoblockers.

Dexrazoxanum is antidotum to antracycline antibiotics. Antracycline antibiotics chelate with iron and dexrazoxanum disturbs chelates formation and has antioxidant properties.

Treatment of ethanol overdosage consists of intensive supportive care with special attention to preventing hypoglycemia and ketoacidosis.

The treatment of barbiturate overdosage is mainly supportive. Maintenance of cardiopulmonary stability is of prime importance. Lavage or emesis can be attempted if proper precaution has been taken to avoid aspiration. Gastric lavage is contraindicated in the comatose patient. Since most barbiturates are acidic, alkalization of the urine and the promotion of diuresis are often beneficial. Hemodialysis is the most effective means of treating severe barbiturate overdosage. It tends to be more effective in removing short-acting barbiturates rather than long-acting ones because the degree of protein binding is considerably less. Analeptic agents are contraindicated.

Paracetamololum (Acetaminophenum) overdose can result in liver toxicity. Acetylcysteinum inactivates toxic metabolites.

Acids (e.g. hydrochloric, nitric, sulfuric, sodium bisulfate) Dilution or therapy with water or milk following ingestion is the treatment of choice. In the cases of

acidosis natrii hydrocarbonas is administered.

Alkalies (e.g. sodium hypochlorite, sodium hydroxide, potassium hydroxide) are substances which are found in some household products. Immediate and extensive irrigation of affected areas is recommended. Oral ingestion requires dilution with water or milk. Steroid therapy for a 3-week course has been used when esophageal burns occur. Acidum citricum may be administered intravenously in alkalosis.

Pharmacologic antagonism can be effective with compounds which act at specific receptors (pharmacologic antagonism), but stimulation of physiologic mechanisms may be deleterious (physiologic antagonism); for example, CNS stimulants used in respiratory depression can cause convulsions.

	Drug	Drug forms
1.	Adrenalini hydrochloridum	Flac. 0,1% 10ml; Amp. 0,1% - 1ml
2.	Alloximum	Amp. 0,075
3.	Aminazinum	Tab. (dragee) 0,025, 0,05, 0,1; Amp. 2,5% - 1, 2, 5, 10ml
4.	Apomorphini hydrochloridum	Pulv.; Amp. 1% - 1ml
5.	Atropini sulfas	Pulv.; Amp.0,1% - 1ml;
6.	Hydrocortisoni acetas	Amp. 2,5% - 2ml
7.	Glucosum	Pulv.; Tab. 0,5, 1; Amp. 5%, 10%, 40% - 25, 50ml; Flac. 5% - 200ml, 500ml
8.	Deferoxaminum	Amp. 0,5
9.	Diazepamum	Tab. 0,005; Amp. 0,5% - 2ml
10.	Dinatrii aethylen- diamintetraacetat	Pulv.

11.	Dipiroximum	Pulv.; Amp. 15% - 1ml
12.	Kalii permanganas	Pulv.
13.	Kalii chloridum	Pulv.; Sol. 10% ad usum internum
14.	Calcii chloridum	Amp. 10% - 10ml; Sol. 10% ad usum internum
15.	Acidum aminocapronicum	Flac. 5% - 100ml
16.	Coffeinum-natrii benzoas	Pulv.; Tab. 0,1, 0,2; Amp. 10%, 20% - 1ml
17.	Magnesii oxydum	Pulv.; Tab. 0,5
18.	Magnesii sulfas	Pulv.; Amp. 20%, 25% - 5, 10, 20ml
19.	Mannitum	Flac. 30,0; Amp. 15% - 200, 400, 500ml
20.	Mesatonum	Pulv.; Amp. 1% - 1ml
21.	Methylenum coeruleum	Pulv.; Sol spirit. 1%; Amp. 1% - 20ml, 50ml; Sol. 1%
22.	Nalorphini hydrochloridum	Pulv.; Amp. 0,5% - 1ml
23.	Natrii hydrocarbonas	Tab. 0,3, 0,5; Amp. 3%, 5% - 20, 50ml; Supp. 0,3, 0,5, 0,7
24.	Natrii thiosulfas	Pulv.; Amp. 30% - 5, 10, 50ml
25.	Sol. Natrii chloridi isotonicae	Amp. 5, 10, 20ml; Flac. 400ml
26.	Pentaminum	Amp. 5% - 1ml

27.	Polyglucinum	Flac. 400ml
28.	Proserinum	Pulv.; Tab. 0,015; Amp. 0,05% - 1ml
29.	Promedolum	Pulv.; Tab. 0,025; Amp. 1%, 2% - 1ml
30.	Sol. Ammonii caustici	Flac. 30ml; Amp. 1ml
31.	Strophanthinum	Amp. 0,05% - 1ml
32.	Sulfocamphocainum	Amp. 10% 2ml
33.	Tanninum	Pulv.
34.	Tetacinum-calcium	Tab. 0,5; Amp. 10% - 20ml
35.	Carbo activatus	Pulv.; Tab. 0,25 – 0,5
36.	Unithiolum	Pulv.; Amp. 5% - 5ml
37.	Enterogelum	Flac. 45, 135
38.	Aethimizolum	Pulv.; Tab. 0,1; Amp. 1%, 1,5% - 3, 5ml
39.	Euphyllinum	Pulv.; Tab. 0,15; Amp. 24% - 1ml; 2,4% - 10ml

Cancer Chemotherapy (Antineoplastic agents)

Most of the current clinical **antineoplastic agents** act on the proliferating population of cells; none acts primarily to influence tumor cell invasion or metastases. Combinations of anticancer agents with different mechanisms of action are often used in an attempt to destroy all of the malignant cells. Antineoplastic agents kill a constant fraction

of the tumor cells rather than a fixed number of cells. In an attempt to eliminate all of the malignant cells, cancer chemotherapeutic agents are often administered as an adjunct to surgery or irradiation. Antineoplastic agents generally have a slight selectivity for tumor cells as opposed to normal tissues. Therefore, many of the clinically used antineoplastic agents cause severe toxicity to the patient's normal tissues. Because rapidly proliferating cells are likely to be the ones most severely affected, the common **side effects** are: myelosuppression, gastrointestinal bleeding and ulcers, nausea and vomiting, alopecia, nephrotoxicity, teratogenesis, abortion, and immunosuppression. Anticancer agents can also be carcinogenic.

Classification: The major classes of antineoplastic agents are grouped primarily according to a chemical structure, source, or mechanism of action. There are following eleven major groups:

1. Alkylating agents;
2. Antimetabolites;
3. Derivatives from natural products (Alkaloids);
4. Antibiotics;
5. Hormones and antagonists;
6. Enzymes;
8. Immunomodulating factors and cellular growth factors;
9. Monoclonal antibodies;
10. Drugs from embryonal tissues;
11. Other drugs;

ALKYLATING AGENTS

All of the drugs in this category have or can form an alkyl group which becomes covalently bound to cellular constituents. All alkylating agents are phase-nonspecific. In addition to killing of rapidly proliferating cells, these drugs also kill nonproliferating cells as a result

of alkylating of the RNA, DNA, and essential proteins. **Alkylation of DNA** is responsible for the cytotoxic antitumor activity of most alkylating agents. Enzymes involved in the DNA repair may limit the responsiveness of some tumors to the alkylating agents.

The major classes of alkylating agents are:

- a. Nitrogen mustards;
- b. Nitrosoureas;
- c. Alkyl sulfonates;
- d. Triazenes;
- e. Others.

Nitrogen mustards

Mechanism of action: One chloroethyl moiety undergoes cyclization with the release of a chloride ion. The resulting highly reactive carbonium ion can attack nucleophilic groups on protein, DNA, RNA, and other cellular constituents. As with all alkylating agents, the nitrogen mustards are phase-nonspecific. **Embichinum** (mustargenum, mechlorethamine) was the prototype of the nitrogen mustards, the first clinically used.

Therapeutic uses: It is used to treat Hodgkin's disease and non-Hodgkin's lymphomas. In the treatment of Hodgkin's disease, embichinum is combined with vincristinum, procarbazine, and prednisone. It has also been used topically for the treatment of mycosis fungoides.

Adverse effects: Myelosuppression, nausea and vomiting, alopecia, menstrual irregularities may be observed.

Cyclophosphamide is an essential part of many effective drug combinations. The metabolites **phosphoramide mustard** and **acrolein** are believed to be the final cytotoxic species.

Therapeutic uses: Cyclophosphamide is used alone and in

combination with other agents in the treatment of a variety of neoplastic disorders, including: Hodgkin's disease, Burkitt's lymphoma, ovarian and breast carcinomas, oat cell lung cancer, neuroblastoma. Cyclophosphamidum has also been used as an immunosuppressing agent for organ transplants.??

Adverse effects: Unlike other nitrogen mustards, Cyclophosphamidum rarely induces thrombocytopenia. Alopecia occurs frequently but is modest. Hemorrhagic cystitis, which is probably due to chemical irritation of the bladder mucosa by the metabolite acrolein. A liberal fluid intake dilutes the urinary concentration of acrolein and decreases this side effect. Prolonged Cyclophosphamidum treatment can occasionally produce interstitial pulmonary fibrosis. Prolonged use has also resulted in fatal cardiomyopathy, especially when Cyclophosphamidum was used with other cardiotoxic drugs.

Ifosfamidum (ifex) is an analogue of cyclophosphamidum which requires metabolic activation to form 4-hydroxy ifasfamidum. It is active against a broad spectrum of tumors, including germ cell cancers of the testis, lymphomas, sarcomas and carcinoma of the lung, breast, ovary. It is more active than cyclophosphamidum in germ cell cancers and sarcomas.

Sarcolysinum (melphalanum, alkeranum)

Major use of sarcolysinum is the treatment of multiple myeloma, but it is also used for the treatment of breast and ovarian cancer.

Adverse effects: prominent myelosuppression, nausea, vomiting, and alopecia are rare.

Chlorbutinum

Therapeutic uses: Chronic lymphocytic leukemia, Waldenström's macroglobulinemia, Hodgkin's disease and non-

Hodgkin's lymphomas.

Adverse effects: myelosuppression, nausea, vomiting.

Dopanum has the same therapeutic use and adverse effects.

Nitrosoureas

Mechanism of action: In aqueous environments the nitrosourea derivatives decompose to alkylating and carbamylating intermediates. The therapeutic and toxic effects of the nitrosourea derivatives are due to both the alkylation of DNA and other nucleophiles and the carbamylation of lysine residues on proteins. The consequences of the DNA alkylation by means of the nitrosourea derivatives are similar to those seen with other alkylating agents. The **high lipid solubility** of some of the nitrosoureas allows penetration of the blood-brain barrier and are useful in the treatment of malignancies of the CNS. The nitrosoureas are proliferation-independent.

Carmustinum

Therapeutic uses: Hodgkin's disease and non-Hodgkin's lymphomas, meningeal leukemia, tumors of the brain, multiple myeloma, malignant melanoma.

Adverse effects: delayed hematopoietic depression, nausea and vomiting, the CNS toxicity, pulmonary fibrosis

Lomustinum has similar therapeutic uses and adverse effect.

Alkyl sulfonates (Ethylenamines)

The prototypic agent is **Myclosanum (busulfanum)**.

Mechanism of action: Cleavage of the alkyl-oxygen bond in is myclosanum produces an electrophile, which forms intrastrand DMA cross-links.

Therapeutic uses: Granulocytic leukemia, Waldenström's macroglobulinemia.

Adverse effects: Myelosuppression is common. Endocrine

disfunction , including impotence, sterility, and amenorrhea, can occur. Hyperuricemia can result from rapid purine catabolism. Skin pigmentation and pulmonary fibrosis have been noted.

Triazines (The prototype is **dacarbazine**).

Mechanism of action: Dacarbazine is demethylated by microsomal enzymes and functions as an alkylating agent. The active species has a methyl carbonium ion which can methylate the DNA and RNA and inhibits the synthesis of the DNA, RNA, and protein.

Therapeutic uses: Dacarbazine is one of the most active agents against malignant melanoma. It is also used for soft-tissue sarcomas and Hodgkin's disease.

Adverse effects: nausea, vomiting, myelosuppression, neurotoxicity

Others – **Temozolamidum (temodalum)** is a neoplastic agent, imidazotetrazene derivative with alkylating activity. It is used in glioma, melanoma.

ANTIMETABOLITES

The antimetabolites are structurally similar to endogenous compounds and are antagonists of folic acid (**methotrexatum**), purines (**mercaptopurinum, thioguaninum, fludarabinum, pentostalinum, cladribinum**), or pyrimidines (**fluorouracilum, cytarabinum**). Antimetabolites are drugs acting primarily in the S phase of the cell cycle. In addition to their cytotoxic effects on neoplastic cells, the antimetabolites also have immunosuppressant actions. Antimetabolites are compounds which bear a structural similarity to a naturally occurring substance, such as a vitamin, nucleoside, or amino acid. The antimetabolite competes with the natural substrate for the active site on an essential enzyme or for an important receptor. Some antimetabolites can be incorporated into DNA or RNA and, thus, can disrupt cellular function. Most antimetabolites are phase-specific and act during DNA synthesis.

There are three major classes of antimetabolites:

1. Folic acid analogues (primarily methotrexatum);
2. Pyrimidine analogues;
3. Purine analogues and related inhibitors.

Methotrexatum is a folic acid analogue which competitively inhibits dihydrofolate reductase, the enzyme which catalyzes the formation of tetrahydrofolate from dihydrofolate. Normally, tetrahydrofolate is converted to a variety of coenzymes which are necessary for one-carbon transfer reactions involved in the synthesis of purines, thymidylate, methionine, and glycine. Methotrexatum inhibits the formation of these coenzymes. The formation of polyglutamate derivatives of methotrexatum appears to be important

for cytotoxic actions. The primary cause of cell death is the blockade of the biosynthesis of thymidylate and purines required for DNA synthesis. Thus, methotrexatum kills cells in S phase. Because methotrexatum also inhibits RNA and protein synthesis, the drug slows the rate of entry of cells into S phase, and therefore, it is a self-limiting S-phase-specific drug. Substances such as **leucovorinum** (also called citrovorum factor or folinic acid) and **thymidinum** can be converted to the required tetrahydrofolate coenzymes or to thymidylate even in the presence of methotrexatum.

Methotrexatum is used in combination with other agents to treat acute lymphoblastic leukemia, Burkitt's lymphoma, trophoblastic choriocarcinoma, and carcinomas of the breast, cervix, lung, head, and neck. The drug is also useful in the treatment of mycosis fungoides and psoriasis. There is no good rationale for high-dose methotrexatum therapy. At low, pulsed doses, this agent has been used experimentally in the treatment of rheumatoid arthritis.

Adverse effects: Myelosuppression is significant with leucopenia and thrombocytopenia occurring 1-2 weeks after drug administration. Gastrointestinal toxicity is manifested by ulcerative stomatitis and diarrhea and can disrupt therapy. Nausea and vomiting are common acute adverse effects. Prolonged low-dose methotrexatum therapy can cause hepatic dysfunction, culminating in cirrhosis of the liver if drug treatment is not terminated. Renal failure can occur with high doses of methotrexatum due to the precipitation of the drug in the renal tubules. Large volumes of alkaline urine must be maintained to prevent this toxicity. The drug is not administered to individuals with poor renal function. Methotrexatum may cause dermatitis. There have been reports of necrotizing leukoencephalopathy when methotrexatum was given with concomitant radiation therapy.

Purine analogues

Mercaptopurinum and **thioguaninum** are purine antimetabolites. 6-Mercaptopurine is a structural analogue of hypoxanthine. Both drugs are activated by hypoxanthine-guanine phosphoribosyltransferases (HGPRTases) to toxic nucleotides which inhibit several enzymes involved in purine nucleotides.

Mechanism of action: 6-Mercaptopurinum must be converted intracellularly to the nucleotide 6-mercaptopurine ribose phosphate by hypoxanthine-guanine phosphoribosyl transferase (HGPRT). Mercaptopurinum also can be converted to 6-methylmercaptopurine ribonucleotide. Mercaptopurinum ribose phosphate and the methylated nucleotide are cytotoxic primarily because they inhibit purine biosynthesis. Both block the aminotransferase which is responsible for the first step in purine biosynthesis, namely, the formation of 5-phosphoribosylamine, by feedback inhibition. Mercaptopurine ribose phosphate inhibits adenylosuccinate synthetase, the enzyme which converts inosinic acid to adenylosuccinic acid, and inosinate dehydrogenase, the enzyme which converts inosinic acid to xanthylic acid.

Therapeutic uses: Mercaptopurinum is used in the maintenance therapy of acute lymphocytic and acute lymphoblastic leukemia. It is also useful in the treatment of acute and chronic myelogenous and granulocytic leukemia.

Adverse effects: Mercaptopurinum causes myelosuppression, but this is more gradual in onset than the suppression caused by methotrexatum. Mercaptopurinum also causes anorexia and nausea. One-third of treated patients may develop jaundice associated with biliary stasis and hepatic necrosis. Discontinuation of therapy usually reverses this adverse effect. Hyperuricemia and hyperuricosuria may occur with mercaptopurinum therapy. This is

due to the destruction of cells and the release of purines which are metabolized by xanthine oxidase.

Thioguaninum is a structural analogue of guanine has similar mechanisms of action, therapeutic uses and adverse effects.

Pentostatinum is a purine analogue which is a potent inhibitor of adenosine deaminase. Pentostatinum also interferes with the synthesis of nicotinamide adenine dinucleotide, resulting in the DNA strand breakage. Pentostatinum has been used for the treatment of hairy cell leukemia, mycosis fungoides, and chronic lymphocytic leukemia.

Fludarabinum (flurara) is fluorinated purine analogue of the antiviral agent vidarabinum. The active metabolite 2-fluoro-ara-adenosine triphosphate inhibits various enzymes involved DNA synthesis including DNA polymerase-alpha, ribonucleotide reductase, DNA primase. The drug is highly active in the treatment of chronic lymphocytic leukemia, low-grade lymphomas. The major adverse effects are: myelosuppression, nausea, vomiting, neurotoxicity.

Cladribinum (Leusstatinum) is a synthetic purine nucleoside which is converted to an active cytotoxic metabolite by the enzyme deoxycytidine kinase. The drug is highly active against hairy cell leukemia, low-grade lymphoid malignancies. The major adverse effect is myelosuppression.

Pyrimidine analogues

5-Fluorouracil is a fluorine-substituted analogue of uracil.

Mechanism of action: Like the purine antimetabolites, 5-fluorouracil must be metabolically activated to a nucleotide, in this case 5-fluoro-2'-deoxyuridine-5'-monophosphate. There are three general pathways for transformation: 5-Fluorouracil can be metabolized to the deoxyribonucleoside with subsequent

phosphorylation by thymidine kinase. 5-Fluorouracil can be converted to 5-fluorouridine-5'-phosphate by pyrimidine phosphoribosyltransferase and then to the deoxyribonucleoside by ribonucleotide reductase. The conversion of 5-fluorouracil to fluorouridine, which is subsequently phosphorylated by uridine kinase to form 5-fluorouridine-5'-phosphate and so on. The cytotoxicity of 5-fluorouracil is due primarily to inhibition of the DNA synthesis caused by blockage of thymidylate synthetase. Thymidylate synthetase normally transfers a methylene group from reduced folic acid to deoxyuridylate monophosphate (dUMP) to form thymidylate, which is essential for the DNA synthesis. Cytotoxicity may also be due to incorporation of 5-fluorouridine triphosphate into the RNA, which leads to "fraudulent" RNA formation.

Therapeutic uses: 5-Fluorouracil is used in combination with other agents for the treatment of breast cancer. It has palliative activity in gastrointestinal adenocarcinoma. It is also used to treat carcinomas of the cervix, bladder, and prostate. Topical application of the drug has been useful for the treatment of premalignant keratoses of the skin and superficial basal cell carcinoma.

Adverse effects: Myelosuppression, especially leucopenia, frequently occurs. Stomatitis, diarrhea, nausea, and alopecia are seen. Neurologic toxicity occurs in 1%-2% of treated patients.

Cytarabine (cytosine) is an analogue of cytidine in which the ribose moiety has been replaced with an arabinose.

Mechanism of action: Cytarabine must be activated, by pyrimidine nucleoside kinase, to the nucleotide triphosphate, aracytosine triphosphate. The nucleotide triphosphate competitively inhibits DNA polymerase and, thus, blocks DNA synthesis and causes cell death. Cytarabine nucleotides can be incorporated into

DNA and RNA, but the biologic significance of it remains to be established. It is an S-phase-specific agent.

Therapeutic uses: Cytarabine is used to treat acute myelogenous leukemia in combination with an anthracycline or 6-thioguanine. It is also used to treat acute granulocytic and acute lymphocytic leukemias.

Adverse effects: severe myelosuppression; nausea; mucosal inflammation.

NATURAL PRODUCTS

The natural products used in cancer chemotherapy are extracted from a variety of plants and lower organisms.

The major classes of natural products are:

- a. Antibiotics;
- b. Vinca alkaloids;
- c. Enzymes;
- d. Biologic response modifiers;
- e. Epipodophyllotoxins.

Antibiotics

This category of antineoplastic drugs is made up of several structurally dissimilar agents, including **doxorubicin, daunorubicin, bleomycin, dactinomycin, mitomycin, and mithramycin.**

Dactinomycin (actinomycin D) is isolated from a *Streptomyces* species. It contains two cyclic polypeptides which are linked by a chromophore moiety.

Mechanism of action: Dactinomycin binds noncovalently to double-stranded DNA and inhibits DNA-directed RNA synthesis. It is a phase-nonspecific agent.

Therapeutic uses: Dactinomycin is used in combination

with other agents to treat Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma, Kaposi's sarcoma, and soft-tissue sarcomas. It has been used in renal transplantation.

Adverse effects: Dactinomycin produces myelosuppression, nausea, and vomiting. Skin damage can occur in areas of previous irradiation.

Anthracyclines.

Doxorubicinum is the prototype of anthracyclines. Isolated from *Streptomyces*, it contains an amino sugar and an anthracycline ring. Rubomicini hydrochloridum has similar structure. **Daunorubicinum** is structurally almost identical to doxorubicinum, lacking only of a hydroxyl moiety. **Mitoxantronum** is a synthetic anthracycline related to the anthracyclines.

Mechanism of action: The aglycone portion of the drug molecule intercalates with the DNA and RNA. The ionic sugar portion of the molecule bonds ionically to stabilize the intercalation. As a result, the DNA and RNA are distorted during synthesis. There may be some free radical production, which may play a role in tissue cytotoxicity. Mitoxantronum causes less free radical formation and lipid peroxidation than doxorubicinum and theoretically should cause less cardiotoxicity.

Therapeutic uses: **Doxorubicinum** is one of the most effective agents against solid tumors. It is also effective against acute leukemias and malignant lymphoma. **Daunorubicinum** is most effective against acute lymphocytic and granulocytic leukemia. It has little activity against solid tumors. **Mitoxantronum** appears to be as effective as daunorubicinum but may be less toxic when combined with cytarabine for the initial treatment of acute nonlymphocytic leukemia. It may also be effective in some patients with advanced breast cancer.

Adverse effects: Doxorubicinum, daunorubicinum, and mitoxantronum cause both **acute and chronic cardiomyopathy**. The depression of cardiac function resulting from repeated doses limits the total amount of drug which can be administered. Myelosuppression, especially leucopenia, occurs in most patients. Alopecia is a common side effect. Both drugs also cause nausea and vomiting. Dermatitis at the site of previous irradiation can occur.

Idarubicinum differs from its parent compound dannorubicinum by the absence of the methoxy group in the anthracycline ring structure. It has more lipophilic properties and is more potent than previous anthracyclines. Its mechanism of action, indications, adverse reactions are similar to doxorubicinum and dannorubicinum.

Fleromycines.

Bleomycinum.

Clinically used, bleomycinum is a group of glycopeptides extracted from a *Streptomyces* species. The mixture of glycopeptides found in this extract is referred to collectively as bleomycinum. Different types of bleomycinums differ in their terminal amine moieties.

Mechanism of action: The planar end of the bleomycinum molecule intercalates with the DNA. Bleomycinum is a mixture of glycopeptides which generates free radicals which bind to the DNA, cause strand breaks, and inhibit the DNA synthesis. Bleomycin is an antineoplastic drug active in the G₂ phase of the tumor cell cycle. The other end binds ferrous ion and facilitates its oxidation to ferric ion, thereby generating a free radical.

Therapeutic uses: Bleomycinum is used only in combination with other agents. It is effective with cisplatinum and vinblastinum for the treatment of testicular carcinoma. It is also used for Hodgkin's disease and non-Hodgkin's lymphomas and for squamous

cell carcinomas of the head and neck, cervix, and skin.

Adverse effects: Bleomycin causes an age-related and cumulative-dose-related pulmonary toxicity. This consists of a pneumonitis, which can progress to fatal pulmonary fibrosis. Bleomycin does not produce significant bone marrow toxicity.

Actinomycines

Dactinomycin:

Mechanisms of action: Dactinomycin is an antineoplastic drug which binds to double-stranded DNA and inhibits the DNA-dependent RNA synthesis. Dactinomycin can be given parenterally, and both intact drug and metabolites are excreted in the bile.

Therapeutic use: Dactinomycin is used in melanoma and Wilms' tumor.

Mitomycin (mitomycin C)

Isolated from *Streptomyces*, mitomycin contains an aziridine ring as well as a urethane and a quinone moiety.

Mechanism of action: Mitomycin is an antineoplastic drug which is metabolized by liver enzymes to form an alkylating agent which cross-links DNA. Mitomycin is given intravenously and is rapidly cleared via hepatic metabolism. Mitomycin is reduced intracellularly by a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent reductase, and then alkylates the DNA. Thus, it can also be classified as an alkylating agent. Because oxygen-derived free radicals can be formed, single-strand DNA lesions also can occur.

Therapeutic uses; Mitomycin has limited use in the treatment of carcinomas of the stomach and cervix. It is also used to treat superficial carcinoma of the bladder.

Adverse effects: Myelosuppression is a major complication with intravenous administration. Dermal, pulmonary, renal, and

gastrointestinal toxicity may occur. Extravasation can result in severe local injury. Systemic side effects are lessened with intravesical administration.

Vinca alkaloids

The three prominent agents in this group, **vincristinum**, **vinorelbium** and **vinblastinum** are derived from the periwinkle plant.

Mechanisms of action: Vinblastinum and vincristinum are **spindle poisons** which by preventing the assembly of tubulin dimers into microtubules, block the formation of the mitotic spindle. They act primarily in the **M-phase** of the cancer cell cycle. Resistance may occur from increased efflux of the drugs from tumor cells via the membrane drug transporter. Despite their similarity in chemical structure, the alkaloids are quite different in their therapeutic applications and toxicities.

Mechanism of action: Alkaloids bind to tubulin, thereby interfering with the assembly of spindle proteins during mitosis. Agents are **M-phase-specific**, blocking proliferating cells as they enter metaphase.

Therapeutic uses: Vinblastinum is used in combination with bleomycinum and cisplatin for the treatment of testicular carcinoma. It is also effective against lymphomas, neuroblastoma, and Letterer-Siwe disease. Vincristinum is effective against acute lymphoblastic leukemia, Hodgkin's disease, and non-Hodgkin's lymphomas. It is also useful in the treatment of solid tumors in children and tumors of the breast, lung, and cervix in adults. Vincristinum is less likely to cause myelosuppression and is preferred over vinblastinum for use in combination with myelosuppressive agents in the therapy of lymphomas. Vincristinum is used in combination with the corticosteroid prednisone, procarbazine, and an alkylating agent (e.g.

mechlorethamine) in the MOPP regimen for treating Hodgkin's disease. The combination of vincristinum with prednisone is considered the treatment of choice for inducing remission in childhood leukemia. Vinorelbine is particularly useful in the treatment of advanced non-small cell lung cancer and can be administered alone or in combination with cisplatin. It interferes with mitosis in dividing cells through a relatively specific action on mitotic microtubules.

Adverse effects: Vinblastine causes leukopenia within 4-10 days after treatment. Minimal nausea, paresthesias, and jaw pain have been reported. **Vincristine** is significantly neurotoxic with paresthesias and motor weakness being the most prominent effects. These neurologic manifestations are minimized by stopping or reducing the dose at the earliest onset of symptoms. **Vinorelbine** causes severe neutropenia.

Epipodophyllotoxins

Etoposide and **Teniposide** are semisynthetic derivatives of podophyllotoxin.

Mechanisms of action: Etoposide increases degradation of the DNA, possibly via interaction with topoisomerase II, and also inhibits mitochondrial electron transport. The drug is most active in the late S and early G₂ phases of the cell cycle. Teniposide is an analogue with very similar pharmacologic characteristics.

Therapeutic uses: These agents are used in combination drug regimens for therapy of lung (small cell), prostate, and testicular carcinoma, lymphomas, acute myelogenous and lymphoblastic leukemia.

Taxanes Paclitaxel and Docetaxel are isolated from the bark of the Pacific yew tree.

Mechanisms of action: Paclitaxel and docetaxel are spindle

poisons and act differently from vinca alkaloids – they prevent microtubule *disassembly* into tubulin monomers.

Therapeutic uses: The taxanes are used in advanced breast and ovarian cancers.

Biologic response modifiers are agents which act directly on tumor cells or indirectly by enhancing the immunologic response to neoplastic cells. Examples include: **Interleukin-2 (IL-2)**, which is a cytokine secreted by T cells which enhance natural killer cell activity. It is being tested alone and in combination for treatment of melanoma and renal cell cancer. **Interferons (alpha, beta, gamma)**. Alpha interferons have been approved for the treatment of hairy cell leukemia and Kaposi's sarcoma in patients with acquired immune deficiency syndrome (AIDS). Additionally, it is effective for condylomata acuminates.

HORMONES AND ANTAGONISTS

Hormonal therapy relies upon the presence of receptors for endogenous hormones required for cell proliferation. Unlike agents in the other classes of antineoplastic drugs, members of this class generally do not cause severe toxicity.

Tamoxifenum is a nonsteroidal compound.

Mechanism of action: Some tumors, notably breast carcinomas, require estrogen for cell proliferation. Estrogen binds to a cytoplasmic protein receptor, and the receptor-hormone complex translocates into the nucleus, inducing the RNA synthesis. Estrogen receptors are found in two-thirds of the breast tumors which occur in postmenopausal women. Tamoxifenum, an estrogen receptor antagonist, is useful in women whose tumors contain estrogen receptors. Tamoxifenum competes with estrogen for the cytoplasmic receptor, although it has little or no estrogenic activity. The **antiestrogen action** of tamoxifen blocks the growth-promoting

effects of estrogen in estrogen-dependent tumors.

Therapeutic uses: Tamoxifen is used for palliative treatment of advanced breast carcinoma in the postmenopausal woman. Although the response rate has been favorable in both estrogen receptor-rich and receptor-poor forms of breast carcinoma, the response is more favorable in the receptor-rich variant. The tumor reappears upon withdrawal of the drug.

Adverse effects: Hot flashes, mild fluid retention, and nausea occur frequently. With high doses, corneal and retinal opacities have been observed. Hypercalcemia can occur. Toxicity includes nausea and vomiting, hot flashes, vaginal bleeding, hypercalcemia, ocular dysfunction, and peripheral edema. **Toremifenum** is a newer estrogen receptor antagonist used in advanced breast cancer.

Estramustinum phosphate sodium (Emcyt) is a hybrid structure combining estradiol and nitrogen mustard in a single molecule. The drug is used in prostatic carcinoma.

Adverse effects: Breast tenderness, gynecomastia, fluid retention, mild nausea, increased risk of thrombophlebitis and pulmonary embolism. The drug is not myelosuppressive.

Androgens and antiandrogens

Androgens have been used in the treatment of breast carcinoma in postmenopausal women. A number of androgens are available, such as **fluoxymesterone**, **dromostanolone**, and **testosterone**. All are equally active and usually produce a response within 2 months. Common side effects are masculinization and fluid retention.

Antiandrogens (flutamide).

Flutamide is an oral antiandrogen used concurrently with an analogue of luteinizing hormone-releasing hormone (LH-RH), such as leuprolide for the treatment of metastatic prostate cancer.

Flutamidum prevents adrenal androgens from binding to androgen receptors in the prostate gland and in prostate cancer cells. Flutamidum frequently causes gynecomastia and may cause hepatitis.

Aromatase Inhibitors: Anastrozolum and letrozolum inhibit aromatase, the enzyme which catalyzes the conversion of androstenedione (an androgenic precursor) to estrone (an estrogenic hormone). Both drugs are used in advanced breast cancer. Toxicity includes nausea, diarrhea, hot flushes, bone and back pain, dyspnea, and peripheral edema.

Adrenal corticosteroids

Corticosteroids inhibit cellular protein synthesis and also attach to specific corticosteroid-binding proteins associated with leukemia cells. **Prednisonum**, a glucocorticoid, has been used successfully in combination with cytotoxic agents in the treatment of lymphoblastic and chronic lymphocytic leukemia. Other glucocorticoids are also active in combination with other cytotoxic agents in the treatment of Hodgkin's disease, non-Hodgkin's lymphomas, and multiple myeloma. Because of their ability to suppress androgen production by suppressing the adrenal cortex, corticosteroids (e.g. prednisolonum) have also been used in the treatment of breast carcinoma.

Progestins

Progestins bind to cytosolic progesterone receptors and cause maturation of the endometrium to a nonproliferating secretory state. Thus, progestins are sometimes used in the therapy of metastatic endometrial carcinoma which can no longer be treated with irradiation or surgery. The progestins most commonly used as antitumor agents are **medroxyprogesteronum**, which is given intramuscularly, and **megestrolum**, which is given orally. Progestins

also have some limited use in the treatment of metastatic renal cell carcinoma. The mechanism of action in this tumor type is unclear. The progestins cause mild fluid retention and vaginal bleeding.

Gonadotropin-Releasing Hormone Analogues: **Buserelinum, Leuprolidum, Goserelinum, and Nafarelinum** are GnRH agonists, peptide analogues. When administered in constant doses so as to maintain stable blood levels, they *inhibit* release of pituitary LH and FSH. These agents are effective in prostatic carcinoma and cause fewer adverse effects. Leuprolidum may cause bone pain, gynecomastia, hematuria, impotence, and testicular trophy.

Somatostatinum analogues – octreotide acetate (sandostatinum) is a synthetic peptide analogue of the hormone somatostatin. Its action include inhibition of the pituitary secretion of growth hormone and inhibition of pancreatic all secretion of insulin and glucagons. Octreotide is useful in inhibiting the secretion of various antacids and peptide hormones by metastatic carcinoid tumors (serotonin) and itself all carcinomas of the pancreas.

Adverse effects: nausea, pain in the injection site, hypoglycemia, hyperglycemia.

Enzymes. L-Asparaginase catalyzes the hydrolysis of asparagine to aspartic acid and ammonia. Depriving the malignant cell of asparagine results in cessation of protein synthesis and cellular death. It has exhibited modest success in the treatment of acute lymphocytic leukemia.

Other drugs

Animal origin drugs: Propesum – complex of peptides and aminoacids obtained as results of proteolysis of

embryonic animals proteins. Propesum inhibits development of tumors and causes their resorption. It stimulates immunoresistanty and metabolism. It is used in complex chemotherapy.

Erbisolum – complex of natural organic compounds from embryonic animal tissues. It has immunomodulate action, inducts interferon and tumor necrosis factor's synthesis. It is used in complex chemotherapy.

Monoclonal Antibodies: Rituximab is a monoclonal antibody to a surface protein in non-Hodgkin's lymphoma cells. It is presently used with conventional anticancer drugs (e.g. cyclophosphamide plus vincristine plus prednisone) in low grade lymphomas. **Trastuzumab** is a monoclonal antibody to a surface protein in breast cancers which overexpress the HER2 protein. Acute toxicity of these antibodies includes nausea and vomiting, chills, fevers, and headache. Rituximab use is associated with hypersensitivity reactions and myelosuppression. Trastuzumab may cause cardiac disfunction , including congestive heart failure.

Hydroxyurea is a derivative of urea.

Mechanism of action: Hydroxyurea inhibits ribonucleotide reductase. This enzyme is crucial to the biosynthesis of deoxyribonucleotides which are essential for the formation of the DNA. Hydroxyurea is specific for the S-phase of the cell cycle.

Therapeutic uses: Hydroxyurea is an alternative to busulfan in the treatment of chronic myelogenous leukemia. Hydroxyurea will reduce high white blood cell counts in patients with acute myelogenous leukemia. Other uses include polycythemia vera, essential thrombocytosis and hypereosinophilic syndrome.

Adverse effects: Reversible myelosuppression is the major adverse effect. Gastrointestinal and cutaneous disturbances occasionally occur.

Procarbazine is a substituted hydrazine derivative with a structure similar to which of some monoamine oxidase (MAO) inhibitors.

Mechanism of action: Procarbazine undergoes auto-oxidation and forms hydrogen peroxide, leading to the degradation of the DNA. It also inhibits the DNA, RNA, and protein synthesis.

Therapeutic uses: The major use of procarbazine is in the treatment of Hodgkin's disease, where it is used in combination with mechlorethamine, vincristine, and prednisone (i.e. in the MOPP regimen). Procarbazine also has some activity in the treatment of oat cell carcinomas.

Adverse effects: Leukopenia and thrombocytopenia occur commonly. Gastrointestinal adverse effects as well as potentiation of other CNS-dependent drugs can occur. Since procarbazine is a weak MAO inhibitor, hypertensive reactions can occur when sympathomimetics, tricyclic antidepressants, or foods with a high tyramine content are ingested concomitantly.

Mitotane is a derivative of the insecticide DDT.

Mechanism of action: Mitotane selectively destroys normal and neoplastic adrenocortical cells. It rapidly lowers adrenocorticosteroid levels.

Therapeutic uses: Mitotane is used as palliative treatment for inoperable adrenal carcinoma.

Adverse effects: Gastrointestinal disturbances, lethargy, and dermatitis occur. If patients have Addison's disease, or if shock or trauma occur during mitotane therapy, adrenocorticosteroid replacement is indicated.

Cisplatin is an inorganic platinum coordination complex with a planar configuration. Only the *cis*-isomer is active.

Mechanism of action: Cisplatin binds to the DNA,

causing both interstrand and intrastrand cross-linking similar to the actions of the bifunctional alkylating agents. It also binds extensively to nuclear and cytoplasmic proteins. Cisplatin is a phase-nonspecific agent.

Therapeutic uses: Cisplatin is one of the most effective agents against solid tumors. It is effective alone and in combination with bleomycin and **vinblastine** in the treatment of testicular tumors. Cisplatin is also very useful in the treatment of ovarian carcinoma.

Adverse effects: Dose-dependent impairment of renal tubular function can occur, so that cisplatin should not be used in patients with impaired renal function. High-frequency hearing loss can occur. Severe nausea and vomiting are almost inevitable. Anaphylaxis has occurred.

Carboplatin is chemically, in mechanism of action, therapeutic uses, adverse effects related to cisplatin.

Immunomodulating agents

Recombinant IL-2 (Proleukinum) is a lymphokine which stimulates growth of T lymphocytes. Its use is still considered experimental. The incubation of peripheral T lymphocytes with IL-2 produces lymphocyte-activated killer cells which lyse several types of tumor cells in vitro. IL-2 plus the killer cells has caused regression of metastatic tumors in animals.

Therapeutic uses: IL-2 may offer some benefit to a small number of patients with metastatic renal cancer or melanoma.

Adverse effects: Fever; fluid retention leading to pulmonary edema; hypotension; capillary leak syndrome; cardiac arrhythmias; disorientation.

Interferon alpha-2b (intronum A) is a recombinant DNA product derived from interferon alpha-2b gene of human white

blood cells. Its mechanism of antitumor action involves binding to a plasma membrane receptor. It is useful in the treatment of rare form of chronic leukemia, hairy cell leukemia but has minimal antitumor activity in most human cancers.

Adverse effects: fever, flulike syndrome of muscle ache, fatigue, headache, anorexia, nausea. Other less common effects include leucopenia, diarrhea, dizziness, skin, rash. Cellular growth factors (Filgrastinum, Sargramostimum est.??) are used to accelerate recovery of neutrophils after chemotherapy, to prevent infections, to shorten the duration of neutropenia in patients in whom infections have developed.

There are new drugs - **imantinib mesylate (Gleeved)** inhibitor of the tumor specific receptor. Kinase is used in leukosis; **Herceptin (Trastusumab)** is a humanized antibody directed against the specific antigen on the tumor cell surface and is used in breast cancer.

Principles of Combination Therapy

Chemotherapy with combinations of anticancer drugs usually increases log kill markedly, and in some cases synergistic effects are achieved. Combinations are often cytotoxic to a heterogeneous population of cancer cells and may prevent development of resistant clones. Drug combinations using CCS and CCNS drugs may be cytotoxic to both dividing and resting cancer cells. The following principles are important for selecting appropriate drugs to use in combination chemotherapy: each drug should be active when used alone against the particular cancer; the drugs should have different mechanisms of action; cross-resistance between drugs should be minimal; the drugs should have different toxic effects.

	Drug	Drug forms
	Methotrexatum	Tab. 0,0025;

		Amp. 0,005, 0,05, 0,1
	Mercaptopurinum	Tab. 0,05
	Phthoruracilum	Amp. 5% - 5ml
	Dopanium	Tab. 0,002
	Sarcolysinum	Tab. 0,01; Flac. 0,02, 0,04
	Cyclophosphamidum	Tab. 0,05; Amp. 0,2
	Chlorbutinum	Tab. 0,002, 0,005
	Myelosanum	Tab. 0,002
	Vincristinum	Amp. 0,0005
	Colchaminum	Tab. 0,002, ung. 0,5% - 25,0
	Doxorubicini hydrochloridum	Flac. 0,01; 10ml
	Phosphoestrolum	Tab. 0,1; Amp. 6% - 5ml
	Prednisolonum	Tab. 0,001, 0,005
	Asparaginasum	Flac. 3000, 10000 IU
	Propesum	Amp. 2ml

	Erbisolum	Amp. 1ml, 2ml
	Cystamini Dihydrochloridum	Tab. 0,2, 0,4
	Enterosgelum	Pulv. 45, 135, 225, 450, 650, 900