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Sumy State University

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GENERAL PHARMACOLOGY

Course of Lectures on Pharmacology

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GENERAL PHARMACOLOGY

Pharmacology is the science about interaction between drugs and human organism. Pharmacology is divided into general and special pharmacology. General pharmacology studies the general laws of drug interaction with human organism. Special pharmacology studies the pharmacological groups of drugs and individual drugs. Both general and special pharmacology are divided into pharmacokinetics and pharmacodynamics.

Pharmacokinetics is the section of pharmacology which studies the influence of human body upon drugs (absorption, distribution, deposition, biotransformation, and excretion from the body).

Pharmacodynamics is the section of pharmacology which studies the action of drugs upon the human organism (biological effects, localization, and mechanism of action).

Drug Pharmacokinetics

Penetration of Drugs through Biological Membranes

Prior the influence upon the target organs, drugs penetrate through some tissue barriers. There are 5 main mechanisms of substance transport through biological membranes (tissue barriers).

1. Simple diffusion through cellular membranes. It is most important mechanism of drug penetration which depends on the concentration gradient of substance. Lipophylic drugs penetrate through cellular membranes by means of simple diffusion. Drug lipophylicity depends on the amount of molecular charge. The higher molecular charge, the worse drug solubility in lipids and vice versa. The degree of drug ionization depends on pH of tissues and fluids. If a drug is the weak acid, it will be weakly ionized in acidic environment and its molecules can easily penetrate through biological membranes by diffusion. Such drug is prescribed right after meal, when a gastric content has extremely low pH. Vice versa, weakly basic drug should be taken orally prior meal or in 1.5–2 hours after meal (when gastric acidity is minimal). Besides, weakly acidic

drugs should be washed down by acidic solutions and weakly basic drugs – by basic solutions (e.g., milk or mineral water).

Plasma pH is 7.4, but different fluids of human organism may have other values. Thus, urine pH of adults at morning is 4.8, at evening – 7.4. Therefore, weak acids (e.g., aspirin) are reabsorbed better from the morning urine that provides its retention in the body.

2. Filtration through membrane pores is a secondary way of drug penetration through biological barriers. Pore diameter is small (nearly 4 Å) that makes penetration of larger molecules impossible. Only water and small uncharged water-soluble molecules (urea, sugars) penetrate through pores by means of filtration. The direction of movement depends on concentration difference on both sides of the membrane and on the speed of fluid flow through the membrane.

Drugs with marked polarity are ionized easily and have big charge. These drugs do not penetrate through pores and membranes (e.g., heparin, myorelaxants). Such drugs are administered by means of injection because they are not absorbed in gastrointestinal tract. These drugs cannot penetrate through blood-brain and placental barriers.

3. Facilitated diffusion through membrane is possible for some substances (glucose, amino acids, etc.). This mode of transport is carried out by means of channels with special transporter proteins (permeases). Permeases selectively bind with certain substances and transport them inside of the cells. Facilitated diffusion is possible against concentration gradient.

4. Active transport is characterized by selectivity to certain substances. Unlike facilitated diffusion, active transport needs the use of energy which is released due to ATP hydrolysis. Active transport is carried out against concentration and electrochemical gradients. Thus, some amino acids, nitrogen compounds and their derivatives are transported through membranes by means of active transport.

5. Pinocytosis is the uptake of substances by means of vesicle formation. The substance contacts with part of membrane with following membrane invagination and formation of the vesicle inside

which is the substance. This vesicle is separated from the membrane and transported inside the cell. For instance, some proteins and peptide hormones are transported into the cells by means of pinocytosis.

Routes of Drug Administration

There are enteral and parenteral routes of drug administration. Enteral routes include routes of drug administration through gastrointestinal tract: peroral (oral), sublingual, rectal, and administration into duodenum by means of a feeding tube.

Peroral drug administration is most natural, simple, and comfortable route. But this route is not the best one for the urgent care. In gastrointestinal tract, drug may be changed under the influence of gastric duce and intestinal enzymes. Thus, drug activity is reduced or lost completely. A degree and speed of drug absorption from gastrointestinal tract depends on presence and quality of food, because the food components can slow down the drug absorption due to formation of inactive complexes with it. But, sometimes, the increase of speed of drug absorption under influence of food components is possible.

Most commonly, drugs are taken in 30–40 minutes prior or in 1–2 hours after meal. As a rule, the onset of drug action is in 15–40 minutes after peroral intake. Drugs in coated tablets or in capsules are absorbed in small intestine. Lipid-soluble substances are absorbed after emulsification by bile acids. After absorption, drug is transported through the portal venous system in the liver with the following partial biotransformation. After this, drug enters the bloodstream and starts acting. As a rule, the drug dose for peroral intake is 2–3 times more than for parenteral administration. It is due to drug biotransformation during the first passage through the liver.

Due to the fact that the drug action is developed only when it is entering bloodstream, the term “bioavailability” was proposed. The bioavailability is the part of administered drug dose which reaches the systemic circulation in unchanged form. Bioavailability is given

in the percentage of the administered dose. In intravenous administration, medication bioavailability is 100 %.

When medication is taken sublingually, its absorption develops quickly due to intense blood supply of the mucous membrane of the mouth. The sublingually taken drug does not undergo the influence of gastric juice and gastrointestinal enzymes. Sublingual drug absorption is performed through superior vena cava system that provides the drug entering the bloodstream, bypassing the liver. These factors provide the faster and more marked drug effect than during peroral intake.

Rectal drug administration is used if peroral intake is impossible or for the medication influence on mucous membrane of rectum. This route provides quite fast onset of drug action. Nearly 50 % of rectally administered dose enters inferior vena cava and then the liver. Another part of dose enters the bloodstream bypassing the liver. Therefore, the drug effect in case of rectal administration is 20–25 % higher than in case of peroral intake. A volume of the therapeutic enema is about 25–100 mL. If administered rectally, drug irritates the mucosa, therefore the starch mucus is added to drug solution (in amount 30–50 % of general volume of enema). For the drug influence on rectal mucosa (hemorrhoids, rectal cracks, etc.), the drugs are administered in form of rectal suppositories that provides prolonged local effect.

Parenteral routes of drug administration are used for both resorptive (subcutaneously, intramuscularly, intravenously, etc.) and local (administration into body cavies) effects. Parenteral drug administration is characterized by some advantages: dosing accuracy, fast effect development, less dose in comparison with enteral intake, etc. But along with it, injections can cause contamination (must adhere to sterility), possibility of overdose, or local complications on the injection site (thrombosis, damage of vascular endothelium, etc.).

Intravenous route provides the fast effect and fast appearance of high drug concentration in the heart and CNS (although subsequently the drug redistribution takes place). As a rule, drugs are administered intravenously slowly. The bolus administration, drop-by-drop

administration, and infusion are possible. Non-soluble substances, oil solutions, drugs with marked irritating activity, and drugs provoking blood clotting or hemolysis are not administered intravenously.

Intra-arterial route provides the high drug concentration in the region receiving blood through this artery. Intra-arterial rout is used in treatment of endarteritis and chilblains, for X-ray examination, etc.

Intraosseous drug administration is used in traumatology for regional anaesthesia of extremities, for administration of plasma-substituting drugs (and even blood) in patients with massive burns, including children (administration into the heel bone). The speed of drug effect development for intraosseous administration is approximately the same as for intravenous route.

Intracardial route of drug administration is used in case of the heart arrest. The aim of this administration is to restore the activity of sinoatrial node. Drug injection is accompanied by the following heart massage.

Subarachnoidal route is used for the administration into the spinal canal (with piercing meninges) of such drugs as local anaesthetics, morphine, some antibiotics (for treatment of meningitis). Subarachnoidal injection is performed by an experienced surgeon or anaesthesiologist.

Epidural route provides the drug administration into the spinal canal, but dura must not be pierced. This route is used for anaesthesia of internal organs of the body regions which are located below the level of injection or for pain relief during delivery.

Intraperitoneal drug administration is used seldom. For example, antibiotics may be administered intraperitoneally during the surgery on abdominal organs.

In intramuscular administration, the injection is most commonly made into the external outer quadrant of the sciatic muscle. When administering oil-based solution or suspension, it is necessary to make sure that the needle does not hit a blood vessel. The speed of drug absorption may be increased or decreased by using heat or ice pack.

Subcutaneous route is widely used for administration of different drugs, insulin, and vaccines. Subcutaneous injections are painful.

The speed of subcutaneous drug absorption is lower than in case of intramuscular administration. If intravenous drug administration is impossible (e.g., in patients with extensive burns), subcutaneous administration is used for elimination of dehydration, disturbances of electrolyte balance or acid-base balance, and for parenteral feeding. 1.5–2 L of fluids may be administered subcutaneously during 24 hours. The solutions must be isotonic.

Endolymphatic route provides the drug administration in the lymphatic system. As a rule, the drug is administered in lymphatic vessels of the rear side of the foot, catheterization of which is fulfilled by means of microsurgical techniques. The drug is administered through special batcher at 0.3 mL / min flow rate. The administered solution must be warm. Endolymphatic route is used in diseases which are characterized by active participation of the lymphatic system in pathogenesis (e.g., bacterial infections and prior the surgery for prevention of purulent complications).

Inhaled route of drug administration is used for the influence upon bronchial smooth muscles in patients with asthma, for treatment of purulent infective diseases of bronchi and lungs, inflammation of trachea and pharynx, for oxygen therapy, and for inhaled narcosis. A drug with airflow is administered into the airways by means of inhalers or spray-bottles. The contact between inhaled air and blood provides the fast drug absorption. The effect of the drug depends on its concentration in the inhaled air.

Transdermal route of administration is used for providing resorptive effects of the drugs with marked lipophilic properties. The degree of drug absorption depends on its lipid solubility. The skin lesions (maceration, cracks, etc.) increase the absorption speed. The ability to be absorbed significantly depends on the properties of the ointment base of a drug product. Such ointment bases, as lanoline, pig fat, dimethyl sulfoxide, and spermaceti, increase the transdermal drug absorption. Dimethyl sulfoxide also exhibits anti-inflammatory, antiallergic, and antibacterial effects. Transdermal medicines provide stable drug concentration in the blood for extended time periods.

Nowadays, transdermal drug products are becoming more widespread.

Intranasal route is used mainly for treatment of rhinitis. Medicinal forms for intranasal administration include the nasal drops, ointments, and emulsions. It is necessary to notice that nasal mucosa is characterized by significant blood flow and provides the high degree of drug absorption.

Conjunctival route of drug administration is used in treatment of glaucoma, conjunctivitis, trachoma, initial stage of cataract, etc. Solutions of eye drops, eye ointments, and eye membranes are medicinal forms which are used for application into conjunctival sac.

Drug Distribution in Organism

After absorption in the blood, drugs undergo the uneven distribution in internal organs and tissues. The tissue barriers significantly influence the drug distribution. The tissue barriers include the capillary wall, cytoplasmic membrane, the blood-brain barrier, and the placental barrier.

Most drugs easily penetrate through the capillary wall. Some drugs penetrate through pores by means of filtration; other drugs penetrate through the capillary wall due to diffusion. Some hydrophilic agents are transported through the capillary wall by means of energy called “active transport”.

The blood-brain barrier is the significant obstacle for drug penetration into the central nervous system. The cerebral capillaries have no pores. Pinocytosis also is impossible in them. Besides, the external surface of the vascular endothelium is covered by astroglia that creates the additional barrier for a drug. In general, hydrophilic agents poorly penetrate into the brain, but lipophilic drugs penetrate well. The permeability of the blood-brain barrier increases due to inflammation of the meninges.

The placenta is a significant barrier for drug penetration into the fetus. But lipophilic and some hydrophilic (ionized) agents penetrate through the placenta.

After absorption, a significant amount of the drug binds with plasma proteins, mainly – with albumins. The high degree of binding is typical for sulfonamides of prolonged action, for semisynthetic penicillins and for some other antibiotics and anti-inflammatory agents, etc. The drugs associated with proteins do not penetrate into the tissues, are poorly filtered in kidneys, accumulated in the body, and actually lack pharmacological activity. There is dynamic equilibrium between free drug fraction and associated part of drug. As free fraction penetrates into the tissues, its amount in plasma is maintained due to the drug releasing from the associated fraction.

In intravenous administration, the drug distribution is carried out in two steps. Initially, the drug concentration quickly achieves the maximal level and drug enters tissues together with intensive blood flow (heart, brain, lungs, and kidneys). Figuratively speaking, these organs are taking “the first pharmacological blow”. During the following 10 minutes after injection, the drug is distributed between the blood and the extra vascular fluids and tissues of the body, including organs with low intensity of blood flow (muscles, subcutaneous fat, etc.). In intramuscular and subcutaneous administration, the first phase of drug distribution is weak, because the drug absorption from the injection site and its distribution in the organism occur simultaneously.

The following drug distribution depends on its lipophilic or hydrophilic properties and affinity to certain tissues. Lipophilic agents undergo intensive uptake by fat tissue with depositing in it. Drug release from depot depends on drug excretion and reduction of its concentration in the blood. Some drugs exhibit selective affinity to certain organs and tissues. The drug fraction is released from depot and exhibits its pharmacological effects when the blood drug concentration becomes quite low.

Drug Biotransformation

Most drugs undergo metabolic changes in the organism. This process is called "biotransformation". As a rule, due to metabolic changes, the drug is transformed into water-soluble substance which is easily excreted with urine, bile, or sweat. Polar metabolites are badly dissolved in lipids and characterized by low ability to bind to plasma and tissue proteins. Metabolized drugs badly penetrate through biological membranes and are not reabsorbed by kidneys and intestine.

Drug biotransformation occurs mainly due to hepatic microsomes. Some metabolic changes take place in the intestine, lungs, skin, and plasma. Only some drugs are excreted from the body in unchanged form.

There are two main types of drug biotransformation:

– metabolic transformation;

– and conjugation.

Metabolic transformation is the chemical changes of the substance due to oxidation, reduction, or hydrolysis.

Oxidation is one of the most common ways of drug inactivation. Oxidation occurs in the liver with participation of microsomal enzymes – oxidases. The main representative of oxidases is cytochrome P_{450}. Due to oxidation, the hydrogen atoms are cleaved from the side chains of drug molecules. NADP and oxygen participate in oxidation.

Reduction is the more rare drug metabolism. Such enzymes as nitro- and azoreductases and some others participate in this reaction. Reduction is typical for steroid hormones and their analogues. Such drugs as chloramphenicol, nitrazepam, chloralhydrate, and some others also undergo metabolism by way of reduction.

Hydrolysis is the way for inactivation of ethers and amides. Due to hydrolysis, the ether or amide bond is destroyed. This reaction takes place in the presence of water. Enzymes which catalyze hydrolysis (esterases) are characterized by substrate specificity. Sometimes, the hydrolysis of initially inactive form of drug results in formation of a metabolite with certain pharmacological activity. That

is, the part of modern angiotensin-converting-enzyme inhibitors is prodrugs which are transformed into pharmacologically active agents due to hydrolysis (enalapril is transformed into enalaprilate, fosinopril – into fosinoprilate, etc.).

Conjugation is a reaction of accession of hydrophilic endogenous metabolite to the drug molecule. Previously, endogenous metabolite is activated by formation of macroergic bound at the expense of ATP. Typical reactions of conjugation are the drug binding to the residues of acetic or glucuronic acids, glutathione, sulfates, methyl residue, etc. Conjugation can be the only way of drug biotransformation or can occur after previous metabolic transformation. As a rule, drugs lose the biological activity due to metabolic transformation and conjugation. The drug inactivation is significantly slowed down in patients with hepatic pathology (acute or chronic hepatitis, cirrhosis, etc.). It results in prolongation of drug action and overdose.

Some drugs inhibit the activity of microsomal hepatic enzymes (chloramphenicol, phenylbutazone, etc.) or other enzymes (cholinesterase inhibitors, MAO inhibitors, etc.). It causes the prolongation of action for drugs which are metabolized by means of these enzymes. At the same time, there are drugs which stimulate the synthesis of microsomal enzymes: phenobarbital, ethanol, diazepam, carbamazepine, rifampicin, etc.

Drug Excretion

Drugs and their metabolites are excreted from the body by different ways: together with urine, feces, bile, mother milk, expired air; secreted by sweat, bronchial, and sebaceous glands, etc.

The kidneys play a major role in the drug excretion. The drug excretion depends on the processes of filtration, reabsorption, and secretion. Such substances as water, glucose, amino acids, proteins with molecular weight up to 60,000, and some other substances are filtered in the glomerulus of the kidney nephron. Drug molecules that bind to plasma proteins are not filtered. The filtration speed depends on intensity of renal blood flow. In pathological states with reduced

renal blood flow (shock, glomerulonephritis, etc.), filtration is significantly reduced.

Active drug secretion occurs in the proximal convoluted tubules of nephrons. Secretion through tubular epithelium into the primary urine takes place by means of special transporters with the use of energy. Both free fraction of the drug and fraction associated with proteins may undergo the secretion.

Reabsorption of drugs occurs in distal convoluted tubules. Because drug reabsorption occurs due to passive diffusion through lipid membranes of the epithelial cells, the non-dissociated lipophilic molecules of weak acids or bases and neutral substances are reabsorbed better. Reabsorption depends on pH of urine. Thus, weak acids (barbiturates, benzodiazepines, and sulfonamides) poorly dissociate and are easily reabsorbed in blood if pH of urine is acidic. On the contrary, molecules of weak bases (morphine, atropine, quinine, etc.) dissociate much in the acidic environment and, therefore, are poorly reabsorbed and easily excreted from the body.

Regulation of the urinary pH may be used for treatment of patients with drug overdose and poisoning. Thus, alkalization of urine by means of sodium hydrocarbonate creates the favorable condition for the acceleration of weak acid elimination. And, vice versa, acidification of the urine increases alkaloid excretion because alkaloids are weak bases.

It is necessary to notice that excretion of drugs and their metabolites is significantly slowed down in patients with renal failure. The drugs which undergo mainly hepatic inactivation are preferable for treatment of such patients.

Drugs, which are poorly absorbed in gastrointestinal tract, are excreted with feces. Such drugs are used mainly for influence upon intestinal microflora or as laxative agents.

Some drugs (tetracyclines, penicillins, etc.) are excreted with bile into small intestine, where they undergo either the excretion with feces or secondary intestinal reabsorption (so-called enterohepatic recirculation).

Volatile substances are excreted from the body through lungs. This process occurs due to passive diffusion and depends on frequency and depth of respiration.

Some drugs are excreted with secrets of exocrine glands (sweat, salivary, gastric, etc.).

Some alkaloids are secreted into the stomach cavity, where they undergo the secondary absorption in the blood (e.g., morphine). Therefore, multiple gastric lavages are necessary in treatment of patients poisoned by such alkaloids.

The drug excretion with mother milk (anticoagulants, tranquilizers, cytostatic agents, etc.) is a danger to child.

The process of clearing the organism from the drug is called elimination. For estimation of elimination is used value of "half-life of elimination" or "plasma half-life" ($T_{1/2}$). Half-life of elimination is the time during which the drug plasma concentration is decreased 2 times from its maximum concentration.

It is necessary to notice that an increase of a drug dose results in the lower rate of drug elimination, therefore, the drug's plasma half-life increases.

Besides, the term "clearance" is used for quantitative characteristic of the rate of drug elimination. Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time (eg., mL / min, L / h). There are general, renal, and hepatic clearances.

Drug Pharmacodynamics

Types of Drug Action

Some drugs can act at the place of their application. Such type of drug action is called local action. Such medicinal forms as pastes, ointments, and compresses act locally. But pure local action is very seldom, because some amount of drug is absorbed through skin and mucosa into the blood.

Action of the drug after its absorption into the blood is called resorptive action.

Both in local and in resorptive action, the drug can influence the substrate directly (direct action), or indirectly – through another organ or system (indirect action).

Reflex action is an example of indirect action, when the changes of activity of neural centers or internal organs develop due to drug influence upon some receptors. Thus, the use of mustard plasters, irritating skin receptors, results in relaxation of vessels in some tissues and in improvement of their trophism.

The drug action can be nonspecific (general) or specific (selective). Drugs with nonspecific action influence the functions of many organs and tissues. For example, adaptogens are characterized by nonspecific action. The drugs with specific action influence the function of certain organ or tissue. For example, aerosol of salbutamol influences the bronchial smooth muscles and is used for treatment of bronchial asthma. Because the pure selective action is practically impossible, the term “selective action” is commonly replaced by the term “predominant action”.

There are main and secondary actions of drugs. The main action is a drug action which provides therapeutic effect. For example, cardiotonic action of cardiac glycosides upon the heart provides their curative effect in treatment of patients with chronic and acute heart failure. Simultaneously, cardiac glycosides improve renal blood flow. It is an example of secondary action of cardiac glycosides.

Depending on the strength of the bond between the drug and receptor, there are reversible and irreversible actions. In case of

reversible action, the function of the target organ (tissue, enzyme, etc.) is restored after certain period of time. Reversible action is typical for cholinesterase inhibitors with reversible action (proserinum, etc.). Drugs with irreversible action exhibit the stable effect, when the function of the target organ is restored during long time or is never restored. Irreversible action is typical for organic phosphorus compounds, blocking acetylcholinesterase in cholinergic synapses.

The pharmacological effect develops due to interaction of a drug with certain receptors. Receptors are macromolecules which can interact with the drug with the following change in the cellular activity. There is a large number of different receptors: cholinergic, adrenergic, dopaminergic, serotoninergic, and other receptors.

The ability of the drug to bind to the receptor, which determines the formation of the "drug-receptor" complex, is called **affinity**.

A drug is called an **agonist** (**mimetic**) if its interaction with receptors results in certain biological effects. As a rule, these biological effects are stimulating. If due to interaction with the receptor the drug produces a maximal effect, this drug is called a **full agonist**. A drug producing a partial effect is called a **partial agonist**.

A drug is called an **antagonist** (**blockering drug**) if its interaction with receptors does not result in changes which are typical for stimulation of these receptors.

A drug influencing upon one subtype of receptors as an agonist and upon another subtype as an antagonist is called an **agonist-antagonist**. For example, nalorphine is an agonist of δ- and κ-opioid receptors and an antagonist of μ-receptors.

Principles of Drug Dosing

The drug action depends on the dose. A dose is the quantity of the drug which is taken by a patient. A quantity of the drug for the one intake is called the single dose. A quantity of the drug which is taken by patient during a day is called the daily dose. A course dose is the quantity of the drug which is needed for the full course of treatment.

The minimal drug quantity which causes the development of the minimal therapeutic effect, is called a minimal therapeutic dose. However, the minimal therapeutic doses are seldom used in medicine. Usually, clinicians are guided by moderate therapeutic doses. A moderate therapeutic dose is the drug quantity which causes the development of the optimal therapeutic effect in most patients. Sometimes, the highest therapeutic dose of dose is prescribed. A highest therapeutic dose is the greatest quantity of drug, the intake of which does not cause the development of toxic effects. After the range of therapeutic doses, there is the range of toxic doses which is replaced by the range of lethal doses. Accordingly, the minimal, moderate, and highest doses are distinguished in the each dose range.

The maximum therapeutic doses (both single and daily) of strongly-acting and poisonous drugs are given in the State Pharmacopoeia of Ukraine. Recommended moderate therapeutic doses for adults and children are the landmarks in clinicians' work. During the treatment, a clinician corrects the prescribed doses in dependence on the severity of the patient's condition, dynamics of change in symptoms, and patient's sensitivity.

In cases when it is necessary to create the high drug concentration in the human organism, the first dose of the prescribed drug may be higher than the subsequent doses. This dose is called a **loading dose**. The subsequent doses which are used for continuation of treatment are called **maintenance doses**.

Besides curative doses, the **preventive doses** are widely used in medicine in cases when it is necessary to prescribe some drugs for prevention of certain diseases.

The term "breadth of therapeutic action" is closely connected with the term "dose". The breadth of therapeutic action is the range from the minimal therapeutic dose to the maximal therapeutic dose inclusive. The broader is therapeutic action, the greater is safety of the drug that provides for clinician the higher ability to choose the optimal therapeutic dose for a patient.

Also, the term “therapeutic index” is used to define the drug safety. Therapeutic index is the ratio of moderate lethal dose (LD_{50}) to moderate therapeutic dose (ED_{50}) in animal studies:

$$\text{Therapeutic index} = LD_{50} / ED_{50},$$

where LD_{50} is a dose that causes the death of 50 % of experimental animals and ED_{50} is a dose causing the pharmacological effect in 50 % of animals. The larger the therapeutic index, the safer the drug is.

A physician should always remember the Arndt-Schulz rule formulated by Hugo Paul Friedrich Schulz and Rudolf Arndt. It states that for every substance, small doses stimulate, moderate doses inhibit, and large doses kill. That is, small doses stimulate the functions of vital elements, moderate doses increase them, high doses inhibit the functions, and excessive doses paralyze them.

Phenomena Occurring due to Repeated Drug Administration

The repeated drug administration can result in both the increase and the decrease of the drug effect. An increase in effectiveness of the drug is the result of drug ability to accumulate in the body. This phenomenon is called **cumulation**.

There are both **material** and **functional cumulation**. Material cumulation is the accumulation of drug itself in the body. It is determined by the delay in drug biotransformation and its slow excretion. A possibility of cumulation arises when the drug binds to some substrates and undergoes slow metabolism. Cumulation can cause intoxication. The high degree of cumulation is typical for cardiac glycosides, indirect anticoagulants, hypnotic drugs, etc.

Functional cumulation is the accumulation of drug effects. A prominent example of functional cumulation is a phenomenon of alcoholism. In alcoholism, the pathological psychical changes due to alcohol abuse, gradually increase up to the development of the acute alcoholic psychosis (delirium tremens). Ethyl alcohol itself does not accumulate in the body due to repeated drinking, because it undergoes fast metabolism and excretion.

For prevention of drug cumulation, the close control of the dynamics of functional changes in the body and the drug dosage regime correlation are necessary.

Tolerance is another phenomenon which can develop due to repeated drug intake. Tolerance is the gradual reduction of drug efficacy due to repeated intake. The following tolerance causes are possible: reduction of drug absorption, decrease of receptor sensitivity to the drug, activation of additional metabolic ways instead of those blocked by the drug, acceleration of drug biotransformation (due to induction of microsomal enzymes), rate increase of drug excretion from the body, amplification of homeostatic regulatory mechanisms, etc. If tolerance has developed, the increase of drug dose is necessary for achievement of initial drug effect. Also, it is possible to replace used drug by other medications. But it is necessary to notice, that cross-tolerance is also possible. In this case, tolerance extends to other drugs with similar chemical structure or mechanism of action.

Tachyphylaxis is a special kind of tolerance. It is a very fast tolerance (sometimes after simple drug intake). As a rule, tachyphylaxis develops owing to substrate exhaustion. For example, repeated ephedrine administration causes less elevation in blood pressure if drug is administered repeatedly, with interval 10–30 minutes. It is due to reduction of noradrenaline storage in adrenergic synapses.

In case of sudden discontinuation of drug administration, the **withdrawal** (or discontinuation) **syndrome** can develop. There are two types of the withdrawal syndrome. The first type is typical for a long-term use of hormonal agents. Its essence is in the inhibition of appropriate endocrine glands. Particularly, this type of the withdrawal syndrome is typical for glucocorticoids (prednisolone, dexamethasone, etc.). According to negative feedback, a therapy with glucocorticoids results in the adrenal gland atrophy and reduction of endogenous glucocorticoid synthesis. After cessation of glucocorticoid therapy, the restoration of adrenal gland activity lasts from several months to a year or more. Therefore, sudden

glucocorticoid therapy discontinuation is accompanied by acute adrenal insufficiency with shock-like symptoms. An administration of hormonal drugs is necessary for elimination of these symptoms. To prevent the discontinuation syndrome, the glucocorticoid removal should be slow, with gradual reduction of the dose and frequency of drug administration.

The second type of the withdrawal syndrome develops when the sudden cessation of the drug intake is accompanied by the development of the rebound syndrome. The essence of this phenomenon lies in the fact that cessation of drug intake is accompanied by disinhibition of the regulatory processes which were inhibited by the drug. A hypercompensation with acute aggravation of the main disease develops in this case. To prevent the rebound syndrome, the phasing out of the drug is used when both the dose and the frequency of the drug administration are gradually decreased.

Some drugs cause the development of the **drug dependence** due to repeated intake. There are psychical and physical drug dependences. Psychical drug dependence is manifested by changes in the patient's mind with the following desire to take the drug repeatedly. Psychical dependence develops due to the use of psychosedative drugs which create the feeling of mental comfort, sedation, relaxation, fast and easy way to fall asleep, and imaginary elimination of life conflicts. A rejection of such drugs is accompanied by discomfort, psychical tension, fear, anxiety, uncertainty, etc. A desire to get rid of these feelings makes an addicted person to take drugs again and again. Furthermore, the taken dose should be constantly increased owing to the development of tolerance.

Psychical dependence in people develops also to drugs with stimulating action (amphetamine, sydnocarbum, caffeine, etc.). These drugs cause feeling of tidal forces, activity, euphoria, overestimation of their own capabilities, etc. A desire to keep this condition makes people take psychostimulants. A cessation of such drug use is accompanied by depression, mood decline, reduction of capacity to work, etc. Such dependence is called toxicomania.

Physical drug dependence develops due to metabolic restructuring in the organism under the influence of certain drug. That is to say, such drug became essential for function of some organs and systems. The physical dependence is more severe substance dependence. It develops due to the use of opioid analgesics (morphine, promedolum, heroin, etc.), hypnotic drugs, and some other drug groups.

In persons with physical dependence, a cessation of drug intake causes severe conditions with functional disturbances of different organs and systems (convulsions, loss of consciousness, abdominal pain, nausea, vomiting, respiratory depression, etc.) and even death in patients. A complex of these symptoms is called a withdrawal syndrome or abstinence. Addiction consequences are well known to everybody: the development of drug trafficking, personality destruction, spreading of AIDS, hepatitis, etc.

Combined Drug Use

With an aim to reach the best therapeutic result, the combination of several drugs is commonly used in medicine to influence different links of pathological process. But it is necessary to notice that such combined therapy can cause various complications. According to statistics, the quantity of pharmacotherapeutic complications increases proportionally to the amount of the used drugs. To avoid possible complications, a clinician should know peculiarities of drug interactions.

Drug interactions can change both pharmacokinetics and pharmacodynamics of one another. There is the following classification of drug interactions:

1. Pharmacological interaction:
    1.1. Pharmacokinetic interaction.
    1.2. Pharmacodynamic interaction.
    1.3. Physico-chemical interaction in the body.
2. Pharmaceutical interaction.

Pharmacokinetic interaction develops during the use of two or more drugs. Drugs can influence one another at the stages of

absorption, biotransformation, transport, deposition, and excretion from the body.

Thus, intake of absorbents (active carbon) or covering agents (Almagel) worsens the absorption of other drugs.

If taken drugs interact with plasma proteins, the one drug can replace another in the binding to proteins that results in an elevation of the free fraction of the second agent. It can cause toxic effects.

Medications can interact at the biotransformation step. Thus, a use of drugs stimulating activity of hepatic microsomal enzymes (phenobarbital, etc.) can minimize the efficacy of other drugs due to activation of their biotransformation.

In case of pharmacodynamic type, the drugs interact on the level of receptors. An unidirectional effect of two or more drugs is called synergism. There are two main types of synergism: summation and potentiation. In case of summation, the final effect of both drugs is equal to the sum of their individual effects (additive effect, by analogy with arithmetic: $2 + 4 = 6$). When final effect of two or several drugs is more than arithmetic sum of their individual effects, such type of synergism is called potentiation (supra-additive effect: $2 + 4 \rightarrow 10$). Potentiation is more profitable type of synergism. Also, it is possible a variant when final effect is less than arithmetic sum of individual effects of drugs, but more than individual effects of every single drug. It is so-called infra-additive effect ($2 + 4 \rightarrow 5$).

Synergism is widely used in therapy to achieve the necessary effect by enabling the dose of each of the combined drugs to decrease. Unfortunately, synergism is evident not only for therapeutic effects but also for toxic effects.

Drug interaction can be accompanied by reduction of their efficacy. This phenomenon is called antagonism. Like synergism, there are direct and indirect types of antagonism. If two antagonizing drugs influence the same substrate, such antagonism is called direct (e.g., adrenomimetics and adrenoblockering drugs). If one drug inhibits the effect of another but these drugs influence the different substrates, their antagonism is indirect (e.g., the influence of adrenomimetics and cholinomimetics upon the heart).

Besides, there is phenomenon of synergo-antagonism, when some effects of simultaneously used drugs are increased, but other effects are reduced.

Chemical and physicochemical interactions of drugs are possible in human organism. Thus, charged negatively molecules of heparin interact with positively charged molecules of protamine sulfate.

Antagonism is widely used in medicine for reduction of drug side effects and for treatment of acute poisonings. In such cases we say about antidotes.

Although a combined use of drugs is widely used in medicine, an advantage should be given for monotherapy (treatment by one drug) because side effects of a simple drug are more easily predictable and controllable.

Pharmaceutical interaction is possible during processes of drug manufacturing and keeping or due to mixing drugs in one syringe. For example, the mixed in syringe dibazolum with papaverine reduce the effects one of another. A base for pharmaceutical incompatibility of drugs is their chemical and physical properties.

Main Types of Pharmacological Therapy

Etiotropic therapy is an ideal type of pharmacotherapy because suggests the influence upon the disease cause. An example of etiotropic therapy is the antibiotic use for treatment of infections. But it is necessary to notice that there is the limited list of drugs which affect the disease cause.

A main direction of modern pharmacotherapy is the use of drugs influencing upon basic (possibly the initial) mechanisms of disease pathogenesis. It is so-called pathogenetic therapy. A substitutive therapy is the species of pathogenetic pharmacotherapy when certain drugs are prescribed for deficit compensation of corresponding metabolites, enzymes, hormones, vitamins, etc.

Symptomatic therapy is the use of drugs which reduce or eliminate certain disease symptoms (e.g., pain). Although symptomatic therapy does not result in the recovery, this type of

pharmacotherapy is very important and useful (e.g., the use of analgesics in traumas).

Preventive therapy is also important because it is used to prevent certain disease. Thus, antiviral drugs are used with the purpose of preventing epidemics, antiplatelets are used after myocardial infarction with the purpose to prevent platelets aggregation, etc. Preventive therapy is the therapy of future.

Factors Influencing Drug Effects

Age value. Moderate and highest therapeutic doses are prescribed to adults aged from 18 to 60 years. As a rule, a size, weight, and other individual peculiarities of a person are not taken into account. For patients with low stature and for exhausted patients, the doses are decreased. Sometimes, the drug dosage is performed for 1 kg of the patient's weight or for the unit of the body surface area.

Pediatric pharmacology studies the peculiarities of drug action upon the child's body. The less is the child's age, less perfect are his neuronal and humoral regulatory mechanisms, systems of drug inactivation, immunity, etc. Such organism peculiarities influence the health, growth, and development of the child.

Perinatal pharmacology is the special section of pediatric pharmacology. Perinatal pharmacology studies the drug influence upon the fetus from 24 weeks up to labor and upon the newborn up to 4 weeks. The fetus and newborns are especially sensitive to drug action. It is due to the following peculiarities of their organism: low activity of enzymes, which metabolize the drugs, or absence of these enzymes, reduced excretory renal function, increased permeability of the blood-brain barrier, and underdeveloped central nervous system. Microsomal enzyme system of the liver is formed in the newborn up to the end of the second week, but the full development is reached only up to the end of pubescence. Thus, chloramphenicol, antibiotic drug, is very toxic for newborns and can cause their death because their liver lacks the enzymes which are essential for inactivation of this agent.

State Pharmacopoeia contains the highest simple and daily doses of poisoning and powerful drugs that are prescribed to children of different age. Dose calculation for drugs which are absent in Pharmacopoeia is fulfilled according to the following rule: 1/20 part of the adult's dosage is taken for each year of the child's age. It is necessary to notice that such calculations are very approximate because some children, in their weight and stature, may lag behind in development at 1–2 years of age.

Geriatric pharmacology studies the reaction peculiarities of old and senile patients to the medications. As a rule, such patients have not only age changes but also several chronic diseases. In such patients, absorption and excretion of drug slows down owing to worsened blood supply of gastrointestinal tract and kidneys. Hepatic drug biotransformation is slowed; the level of blood proteins is reduced. The body water is decreased, and the fat tissue volume is increased with age. In old age, the adaptive reserves of human organism are sharply reduced; the carbohydrate assimilation is impaired; and the risk of thrombosis, hypoxia, and acidosis is increased. Age-related changes in vascular wall result in the decreased blood flow: cerebral and coronary blood supply is especially reduced. Therefore, for patients after 60 years of age, the doses of most drugs should be decreased by 1/3–1/2 of the adult treatment dose. Even with these amendments, the drug toxicity in elderly patients significantly higher than in middle-aged people. Therefore, if it is possible, herbal medicines and other safe drugs should be used for treatment of elderly patients.

Patient status. Different diseases significantly influence the sensitivity to drugs and their efficacy. Renal and hepatic diseases can cause the retardation of active drug elimination from the organism that increases the complication risks. For their prevention, it is necessary to know the main ways of drug inactivation. Thus, in patients with renal insufficiency, the use of drugs which are inactivated in liver is preferable; in patients with hepatic diseases, preference is given to drugs which are excreted mainly in unchanged form through the kidneys. A frequency of drug complications and

intoxications is higher in dehydrated, exhausted patients and at weakeneds. Sometimes, the sensitivity to drugs is changed owing to certain pathology. Thus, hyperthyreosis is accompanied by the increased sensitivity of myocardium to catecholamines. Also, human organism sensitivity to drugs changes during pregnancy, menopause, etc.

Gender value. Gender-linked differences in pharmacological response have been investigated insufficiently. In comparison with male, female organism is more sensitive to some substances and drugs (nicotine, alcohol, strychnine, hormonal agents, psychotropic drugs, etc.). But, sensitivity of female organism to cardiovascular drugs is less than the male organism. Males need higher doses of analgesics for postoperative pain relief. Often, pharmacotherapy in women should be stopped during menses and for several following days.

Value of genetic factors. Pharmacogenetics studies the hereditary influence on the reactivity of human organism to drugs and other xenobiotics. It is known that some toxic effects of drugs are caused by blockage or absence of certain genes responsible for synthesis of some enzymes metabolizing xenobiotics. Thus, duration of dithylinum action sharply increases (up to 6–8 hours instead of 5–7 minutes) due to hereditary insufficiency of plasma pseudocholinesterase (butyrylcholinesterase). Erythrocyte glucose-6-phosphate dehydrogenase deficiency is widely spread in regions where population suffer from malaria for many centuries. This enzyme deficiency causes erythrocyte hemolysis after intake of certain drugs (acetylsalicylic acid, paracetamol, chloramphenicol, amidopyrine, sulfonamides, nitrofurans, etc.). Such abnormal individual response to a drug due to a genetic anomaly is called drug idiosyncrasy. It develops on the first administration of the drug, even in small doses. As a rule, idiosyncrasy manifests by sharp and turbulent development. Idiosyncrasy can be identified by collecting family history and survey information of the patient's tolerability of drugs in the past. When prescribing new drugs, it is necessary to

control the reaction on the first administration of the drug (especially in childhood).

Value of daily rhythms. A value of daily rhythms has an undoubted importance for the physiological state of the organism. In the waking state, the activity of nervous and endocrine systems is significantly higher than during the sleep. It is reflected in the susceptibility of the organism to different drugs. Chronopharmacology studies the influence of daily rhythms on the organism. Chronopharmacology is divided into chronopharmacokinetics and chrono-pharmacodynamics.

It is proved that the maximum effect of drugs is observed during the period of the maximum human activity, that is, in the daytime. Thus, maximum analgesic effect of morphine is produced at the beginning of the second half of the day. In the morning and in the night, the morphine activity is significantly less. During angina attacks, nitroglycerin efficacy is significantly higher in the morning than during the second half of the day. The drug toxicity also changes in dependence of the day time. Absorption, biotransformation, and other pharmacological peculiarities of drugs can change during the day. It is known, that antimycotic agent griseofulvin is absorbed better at noon. Absorption of lithium carbonate is significantly higher in the daytime than during the night. One should remember that the drug pharmacological effects produced by drugs at certain times of the day can depend on certain pathological states of the organism. Besides the daily rhythms, there are seasonal rhythms – physiological functions of the organism which also influence the drug activity.

Main and Side Drug Effects

The drug action which provides the development of necessary pharmacological effect (blood pressure reduction, pain relief, fewer reduction, etc.) is called main action. However, besides the main effects, all drugs exhibit side effects which are undesirable for the organism. Side effects develop in the range of therapeutic drug doses. Thus, a hypnotic agent chloral hydrate significantly irritates the mucous membranes when used in therapeutic doses. Side effects may

be primary and secondary. Primary side effects arise as a direct result of the drug influence on a certain substrate. That is, nausea and vomiting induced by ether inhalation develop due to irritative action of ether on gastric mucosa. Secondary side effects develop indirectly. Thus, severe destructive pneumonia can develop due to aspiration of vomit into the respiratory tract during ether narcosis.

Side effects have different levels of severity and different degrees of undesirable influence upon organs and systems.

Allergic reactions are among the undesirable side effects. Drugs can serve as allergens (antigens). According to clinical manifestations, there are allergic reactions of immediate and delayed types. Both types depend on sensitization of the organism and changes of cellular and humoral immunity.

Idiosyncrasy is also one of clinical manifestations of drug side effects.

Undesirable effects which arise in the range of toxic doses are called toxic effects. The main cause of toxic effects is drug overdose.

Different medications can exhibit an undesirable influence on the fetus. **Embryotoxic effect** develops during first 12 weeks after fertilization and, as a rule, results in the fetus death. Embryotoxic effect is typical for nicotine, fluor-containing drugs, hormonal drugs (estrogens, progestins, desoxycorticosterone acetate, somatotropin, etc.), barbituric acid derivatives, antimetabolites, etc.

Teratogenic action can develop due to the drug influence on the fetus from the end of the 4^{th} week up to the end of the 10^{th} week. Teratogenic action is manifested by disturbances of tissue differentiation that results in the development of the newborn abnormalities (malformations). For example, intake of hypnotic agent thalidomide by European pregnant women has resulted in the birth of more than 5,000 children with phocomelia (malformation of the limbs), gastrointestinal and genitourinary tract disorders, etc.

Fetotoxic effect is the result of undesirable effects of the drug on the fetus during the later stages of pregnancy. Herewith, a quality of fetus reaction is virtually identical to the reaction of an adult and can

cause the development of severe pathology or death of either a fetus or a newborn.

It is necessary to notice that drugs can influence the fetus even on the step of progenesis by affecting the reproduction and trophism of male and female sex cells and by causing the chromosomal aberrations or gene mutations. Such drug ability to cause the stable damages of cells and their genetic apparatus which is accompanied by genotype change in the child is called **mutagenic action**. Thereby, it is necessary to stop taking any drugs at least 6 month before the planned pregnancy.

Cancerogenic action is the substance ability to cause the development of malignant tumors. Cancerogenic action of drugs can occur in people of any age.

Besides mentioned disturbances, the so-called non-physiological deviations from the norm are possible due to drug undesirable action (e.g., level elevation of uric acid, bilirubin, metabolic acidosis, etc.). It provides the conditions for the development of certain diseases.

GENERAL PRINCIPLES OF TREATMENT OF ACUTE POISONING

According to statistics, acute poisonings are about 40 % of general amount of emergency cases in clinics. Urgent care in intensive care unit was necessary for 25 % of them. Mortality from acute poisonings is about 4 %.

Maximum cases of poisonings (accidental poisoning) occur in children aged from 1 to 4 years. Among adults, there are both accidental and deliberate (suicidal) poisonings. Moreover, suicidal poisonings are common among young people aged from 16 to 20 years and among elderly. The poisonings caused by alcohol, medicines (hypnotic drugs, antihypertensive drugs, etc.), and household chemicals (insecticides, dyes, gasoline, kerosene, antifreeze, etc.) are dominant. During summer, the poisonings caused by such plants as belladonna, Crow's eye, jimsonweed, and

mushrooms (especially, by *Amanita phalloides*) are common. The incidents of substance dependence are widespread among teenagers inhaling insecticides (Chlorophos [Metrifonate], Carbophos [Malathion], etc.), gasoline, kerosene, etc. It is commonly accompanied by severe poisonings with fatalities. It is necessary to notice that poisons containing toluene cause the condition which is similar to action of hallucinogen LSD (lysergic acid diethylamide). Such substances can cause psychical dependence with fast personality degradation.

There are acute and chronic poisonings. The chronic poisonings develop due to repeated intake of small doses of toxic substances and are characterized by slow progressive development of symptoms. A majority of professional diseases caused by toxic substances are chronic poisonings.

Acute poisonings are characterized by sharp onset and fast development (from several hours to several days). In some cases, such poisonings result in the death of a patient. Patients with hyperacute poisonings are isolated when symptoms increase extremely rapidly with the fast death of the patient. For example, a person dies in 15 minutes after parathion intake on an empty stomach.

A treatment of acute poisonings includes the following measures:

- poison elimination from the body;
- poison inactivation;
- symptomatic therapy (maintenance of organism functions).

Elimination of Poison from the Body

Elimination of Unabsorbed Poison

After skin contact with poison drops, it is necessary to rinse soap from the skin with warm water. There are specific antidotes which neutralize the poison or interfere with its influence upon the skin. If poison gets on the conjunctiva or cornea of the eye, it is necessary to rinse them with warm normal saline, milk, or water

during 10–15 minutes. After this, 0.5–1 % dicainum (tetracaine) solution is applied into the conjunctival sack. If phosphorus organic compounds get in the eyes, they should be rinsed with 3 % sodium hydrocarbonate solution.

In cases when solutions of acids or alkalis get in the eye, the washing of the eye by acidic or alkaline solutions is contraindicated due to possibility of eye tissue damage. Such victims should be taken to the ophthalmologist.

In case of snake bite, the cold is applied topically during 6–8 hours. Circulatory procaine blockage is fulfilled above the bite.

Gastric lavage or induced vomiting is used for the poison elimination from the stomach. 5–10 % sodium chloride solution is used (2–4 teaspoon of sodium chloride dissolved in a glass of water) for inducing vomiting. This solution irritates the gastric mucosa accompanied by spasm of pyloric sphincter and the movement delay of poison into intestine. It results in the reduction of poison absorption. Ipecacuanha syrup may be prescribed for children. This syrup induces the vomiting in 5–20 minutes after intake. Also, apomorphine may be administered subcutaneously or intramuscularly to adults or children over 5 years of age. Simultaneously, ephedrine is administered intramuscularly to prevent hypotension.

Inducing vomiting is contraindicated in the following cases:

– in unconscious patients (vomit can get into the respiratory ways and provoke its obstruction or aspiration pneumonia, because such patients have the relaxed epiglottis);

– in patients poisoned by gasoline, kerosene, turpentine, acids, alkalis, phenol, and other substances which irritate mucous membranes (during vomiting the drops of these substances can get into respiratory tract and cause its damage and pneumonia that can result in the death of the patient).

In other cases, gastric lavage should be fulfilled even after vomiting. Gastric lavage is fulfilled several times with interval 3–4 hours until complete purification of stomach from poison. To prevent

body hypothermia, the warm water or solutions are used for gastric lavage. The use of normal saline, Rheopolyglucin, or potassium permanganate for gastric lavage is preferable. If necessary, active carbon or other adsorbents may be added to the mentioned solutions. Also, milk or egg protein solution (12 egg whites in 1 L of boiled water) may be used. But use of milk is contraindicated in poisonings caused by lipid-soluble substances, because butterfat facilitates the poison absorption, relaxes pyloric sphincter, and promotes the poison transition into the intestine.

Some poisons can be secreted from the blood into the stomach, with the following repeated absorption in the blood. It provides the high concentration of poison in the blood during long time. In such cases, gastric lavage is fulfilled 3–4 times and more during 2 days (e.g., morphine and noxyron poisonings, etc.). After gastric lavage, it is necessary to prescribe active carbon or any other absorbent which sorbs the poison residue.

In cases of lipid-soluble poisoning, vaseline oil should be administered (3 mL/1 kg of the patient's weight) before gastric lavage. Also, saline laxative drug is prescribed, and the intestine lavage is fulfilled. Saline laxatives (magnesium sulfate or sodium sulfate) clean both small and large intestines. Vaseline oil dissolves lipid soluble poisons (kerosene, turpentine, gasoline, etc.) but does not promote their absorption.

Also, the siphon enemas are used for elimination of poisons from intestine. For siphon enema, 8–10 L of water is used.

Elimination of Poison from Blood

Before elimination of poison from the blood, it is necessary to provide a patient with fresh air and administration of analeptics (caffeine, aethymizole), or carbogen inspiration. In poisonings caused by irritative substances for prevention of pulmonary edema, a patient should avoid doing sharp movements. Such patients should be warmed and receive inhaled oxygen. For moistening, oxygen is

passed through the water in Bobrov's apparatus. The anti-foaming agents (ethyl alcohol or antifomsilan) are administered to the patient when the symptoms of pulmonary edema develop. After that, measures to eliminate poison from the blood are carried out: forced diuresis, hemodialysis, hemosorption, blood replacement, etc.

Forced diuresis is used for elimination of water-soluble poisons and their metabolites from the blood. It is possible if poisons are badly bind to proteins and lipids in the blood.

Technique of forced diuresis depends on poisoning severity. In mild poisoning, a patient receives a large volume of drinking water and furosemide perorally. The patient should drink the necessary water volume during 8–12 hours. The volume of drinking water should be at least of daily water demand. In case of average poisoning, drugs which are able to bind poisoning are administered intravenously (Neohemodesum, Polyglucinum, Reopolyglucinum, etc.). In case of acid poisoning (barbiturates, acetic acid, salicylic acid derivatives, etc.), 2–4 % solution of sodium hydrocarbonate is also administered intravenously. After that, 10 % glucose solution with potassium chloride is administered intravenously. In severe cases of poisoning, Neohemodesum, Reopolyglucinum, and sodium hydrocarbonate solution are administered during 1 hour. After this, osmotic diuretics (mannitol) or loop diuretics (furosemide) are administered. A volume of fluids administered intravenously should be equal to the volume of excreted urine. In case of super-severe (terminal) poisoning, initially, it is necessary to restore the breathing and the blood circulation. After that, forced diuresis is carried out.

Forced diuresis is contraindicated in patients with acute and chronic cardiovascular failure and patients with disturbances of excretory renal function. Forced diuresis efficacy is reduced in patients over 50 years of age.

Blood substitution is effective when a volume of transfused blood is 1.5–2 times more than a volume of patient's blood. To prevent hypocalcemia, 10 mL of 10 % calcium chloride solution is added to each 500 mL of citrated blood. Blood substitution is

effective if it is carried out during the first hours of poisoning. As a rule, this measure is ineffective if carried out 8–29 hours after poisoning.

Peritoneal dialysis is based on the ability to transport poison from the organism into peritoneal fluid which is located in the abdominal cavity. For peritoneal dialysis, Ringer solution is used together with added glucose and 5 % albumin solution. Sodium hydrocarbonate solution is added in cases of poisoning by acidic compounds. Administered into abdominal cavity, the solution is left for 45–60 minutes. After that, the solution is evacuated with registration of both input and evacuated volumes. Antibiotics are added to the fluid to prevent infection.

Hemodialysis is used for cases of poisoning by substances which do not bind to plasma proteins and in development of acute renal failure. The earlier you start hemodialysis, the better is a chance for success.

Hemoperfusion is a method of filtering the blood when the blood passes throug a column with absorbtive properties aiming at removing specific toxic substances from the blood. The adsorbent substances most commonly used in hemoperfusion are resins and activated carbon. Hemoperfusion is an extracorporal form of treatment because the blood is pumped through a device outside the patient's body. By means of hemoperfusion, not only the poisons that do not bind to plasma proteins but also other poisons may be eliminated from the body.

Inactivation of Toxic Substance

When the toxic substance is known, antidotes are used in the treatment of poisoning. Antidotes are drugs which are used in specific treatment of poisoning. There are 3 groups of antidotes:

1) antidotes which bind poison and prevent the absorption of poison by their presence;
2) antidotes which accelerate the poison biotransformation;

3) antidotes which are pharmacological antagonists.

Antidotes Binding to the Poison and Facilitating Its Excretion from the Body

Unithiol is a representative of this group. This drug binds heavy metals (copper, zinc, bismuth, gold, nickel, chromium, etc.), arsenic, and cardiac glycosides. Formed complexes are easily soluble in water, and therefore quickly excreted through the kidneys. It is necessary to notice that coordination complexes of unithiol with such metals as iron, silver, lead, and cadmium are unstable and undergo fast hydrolysis. Therefore, in cases of poisoning by these metals, unithiol is not used. Unithiol is administered intramuscularly, sometimes orally, or in inhalations. Complexes of Unithiol with metals undergo dissociation in acidic environment that can cause damage of renal tissues. To prevent that, sodium hydrocarbonate is used after unithiol administration. Side effects of unithiol are dyspepsia, headache, and burning mouth syndrome. Convulsions can develop due to unithiol overdose.

Succimer binds heavy metals, arsenic, and cardiac glycosides. The drug is taken orally, administered intramuscularly, or used for inhalations. In severe poisoning, 3–4 mL of 5 % succimer solution is administered intramuscularly.

Tetacinum-calcium (in Ukraine) (Edetate Calcium Disodium) is a chelating agent which interacts with many metals: lead, iron, zinc, copper, chromium, uranium, manganese, vanadium, cesium, etc. Most commonly, Tetacinum-calcium is used in treatment of acute and chronic lead poisoning. The drug is administered intramuscularly, taken orally, or applied locally. For peroral intake, Tetacinum-calcium is prescribed only after poison elimination from the stomach, because its complexes with metals can be easily absorbed. Long-time use of Tetacinum-calcium can result in iron deficiency and hypochromic anemia. This drug is contraindicated in renal failure and hepatic disturbances.

Penicillamin is a derivative of penicillin. Penicillamin is used for treatment of copper and lead poisoning.

Pentacinum is a drug which is used for elimination of radioactive lead, cesium, zinc, tritium, and decomposition products of uranium. Pentacinum is administered intravenously slowly.

Methylene blue transforms about 10 % of hemoglobin into methemoglobin. The drug is used for treatment of cases with poisoning by cyanides, naphthalene, hydrogen sulfide, sulfonamides, etc. Cyanides bind to methemoglobin forming of nontoxic metcyanohemoglobin that is accompanied by restoration of tissue respiration. Also, glucose promotes the inactivation of cyanides.

Antidotes Accelerating Biotransformation of Poison

Sodium thiosulfate is used for treatment of acute cyanide poisoning. The drug reacts with cyanides to produce nontoxic metabolites which are excreted with the urine.

Ethyl alcohol (Ethanol) is used for treatment of methanol poisoning. Ethanol interacts with alcohol dehydrogenase and prevents the formation of formaldehyde and formic acid that cause metabolic acidosis. Also, ethanol prevents blindness which is caused by methanol.

Antidotes – Pharmacological Antagonists

Atropine is used for treatment of cases with poisoning by M-cholinomimetics and cholinesterase inhibitors. Naloxone and naltrexone are antagonists of opiod receptors and are used for treatment of opioid analgesic poisoning (morphine, heroin, etc.). As a rule, antidotes, pharmacological antagonists, interact with same receptors as poisons. Thus, creation of specific antibodies against substances which are the most common cause of poisoning is promising. Sooner the antidotes are administered, the better is the therapy result. In already developed pathology of tissues, organs, and systems, the efficacy of antidote therapy is reduced. Especially low efficacy of

antidotes is in the treatment of patients in terminal stages of poisoning.

Symptomatic Therapy of Acute Poisonings

Symptomatic therapy has especially important meaning in treatment of poisonings caused by substances which have no specific antidotes. First of all, it is necessary to maintain vital functions of the organism – blood circulation and respiration.

In inhibitory breathing, it is necessary to clean the mouth and pharynx from contents. After that, the mechanical ventilation is carried out. If necessary, cough reflex may be provoked. For that, the inserted through the nose catheter is used for irritation of the epiglottis. A 2 % sodium chloride solution or a 3 % sodium hydrocarbonate solution are inhaled for reduction of sputum viscosity. Trypsine or acetylcysteine are inhaled in the presence of purulent sputum. Antispasmodic agents are added to inhaled solutions.

Centrally acting analeptics are used only in cases of moderate inhibition of central nervous system.

An elimination of hypoxia and pulmonary edema are the primary tasks in patients with acute heart failure. Thereto, the fluid pumping from the lungs is fulfilled. Also, antifoam agents are administered (ethyl alcohol or antifomsilan). In Bobrov's apparatus, oxygen is passed through water with added ethanol (10 mL of 30–40 % ethanol). Antifomsilan is used as aerosol or administered (5–8 drops) into the respiratory ways. In the case of progressive hypoxia, the artificial respiration is used. Ganglion blockering drugs are used for decreasing preload and afterload of the heart. Simultaneously, furosemide is administered. It increases diuresis and reduces the circulating blood volume that results in decreasing preload. It is necessary to notice that osmotic diuretics are contraindicated in such cases. Also, cardiac glycosides are administered to a patient. Albumin is used for restriction of fluid transudation into the alveoli.

Prednisolone, calcium gluconate, and antagonists of H_1-histamine receptors (e.g., dimedrolum) are used to reduce vascular permeability.

In cases of acute vascular failure, the therapy is directed to the cause of intoxication. If poison is unknown, the treatment of acute vascular insufficiency is carried out in the following sequence. Prednisolone is administered first, and then plasma or macromolecular plasma-substituting agents are administered. These measures normalize the blood pressure and increase the urine excretion. If hypotension persists, the vasoconstrictors are administered: noradrenaline, mesatonum (phenylephrine), or angiotensinamide. In cases of circulatory centralization, ganglion blockering drugs or dopamine are administered. Ephedrine and adrenaline are contraindicated at poisoning caused by gasoline, kerosene, and turpentine because these drugs can provoke cardiac arrhythmias. If, despite all measures fulfilled, the blood pressure remains low, the administration of noradrenaline or mesatonum is continued on the background of corticosteroids and ganglionic blockering drugs. Simultaneously, sodium hydrocarbonate and trisaminum are administered for elimination of acidosis. Glucose, insulin, and vitamins are administered for metabolism normalization.

Diazepam, sodium oxibutirate, or barbituric acid derivatives are administered in case of hypoxic convulsions. It is necessary to remember that barbiturates are dangerous due to their ability to cause the respiratory inhibition.

In case when marked hypoxia results in brain edema, furosemide, glucocorticoids (prednisolone, dexamethasone), ascorbic acid, and phenobarbital are administered.

Hyperthermia can develop due to hypoxia or poison influence upon the thermoregulatory center. Organism cooling may be carried out by means of the cold which is applied upon the head and regions of large vessels. Also, antipyretic drugs are administered intramuscularly or intravenously together with dibazolum or

benzohexonium (for the increase of heat emission). In severe cases, dimedrolum or diprazine are administered.

An acute hepatic failure commonly develops due to toxic influence of chlorine-containing substances, tetracyclines, phosphorus organic compounds, poison of *Amanita phalloides*, etc. In such cases, a 20–40 % glucose solution is administered together with insulin and vitamins of group B.

Acute renal failure occurs in poisoning by heavy metals, formalin, arsenic, *Amanita phalloides*, hypnotic drugs, etc. In such cases after antidotes administration, the drugs for elimination of water-salt disturbances (plasma, glucose with insulin, isotonic sodium chloride solution), and diuretics (furosemide, mannitol) are administered. Gastric lavage and saline laxative drugs are used for elimination of excessive potassium in patients with anuria. In case of aggravation of patient condition, hemodialysis is carried out.

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ЗАГАЛЬНА ФАРМАКОЛОГІЯ

Конспект лекцій із курсу фармакології
для студентів спеціальності 7.110101 «Лікувальна справа»
денної форми навчання
(Англійською мовою)

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