D.A. Kharkevitch

PHARMACOLOGY

Textbook
for medical students

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Министерство образования и науки РФ

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General pharmacology is the study of the common patterns of drugs pharmacokinetics and pharmacodynamics. **Pharmacokinetics**[1] is the part of pharmacology that deals with compound absorption, distribution in the body, storage, metabolism and excretion (Fig. II.1). The main subject of **pharmacodynamics**[2] is the biologic effects of compounds as well as localization and mechanism of action.

The effects of drugs are the result of their interaction with the organism. Therefore, the basic properties defining physiologic activity of the drugs are not the only thing for consideration. The effect of drugs is also dependent on method of use of these compounds as well as the general condition of the organism to which their action is directed.

The other topics for discussion are the most important types of pharmacotherapy, as well as general patterns of drugs' side effects and toxicity.

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[1] From Greek *pharmacon* — drug, *kineo* — move.
[2] From Greek *pharmacon* — drug, *dynamis* — power.

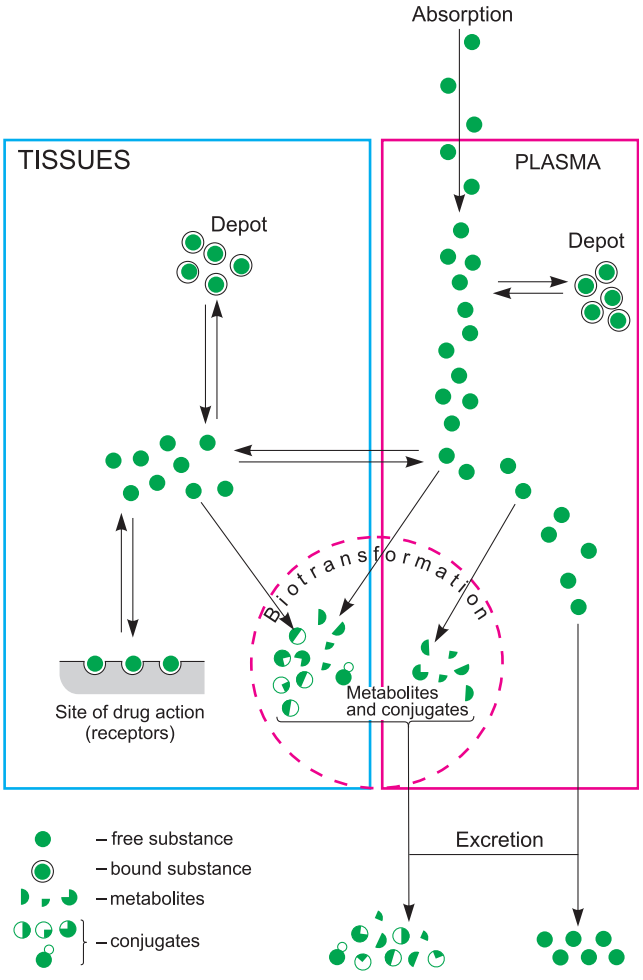

Fig. II.1. Pharmacokinetics of drugs.

1. DRUG ADMINISTRATION ROUTES. ABSORPTION

The usage of drugs for the treatment and prevention of deseases starts with their administration into the organism or application onto the body surface. The route of administration defines the speed of onset of effect, its intensity and duration. In certain cases the route of administration determines how the medications work.

Existing administration routes are usually subdivided into enteral (via digestive tract) and parenteral (not entering into the digestive tract).

Enteral administration comprises oral, sublingual, transbuccal[1], duodenal and rectal routes.

[1] From Latin *bucca* — cheek. A number of drugs are taken transbuccally as polymer pastilles. Their active components are absorbed via the oral mucous membrane.

The most common administration route is oral (by mouth; internally; *per os*). This is the most convenient and simple route of administration. Drugs do not have to be sterile to be administered this way. Absorption[1] of a number of substances (for example, acetylsalicylic acid, barbiturates and other weak electrolytes possessing an acidic nature) occurs partially in the stomach[2] (Fig. II.2). However, the majority of drugs are mainly absorbed in the small intestine. This is a favorable place for absorption due to the large absorbing surface of the intestinal mucous membrane (approximately 200 m^2) and its intensive blood supply.

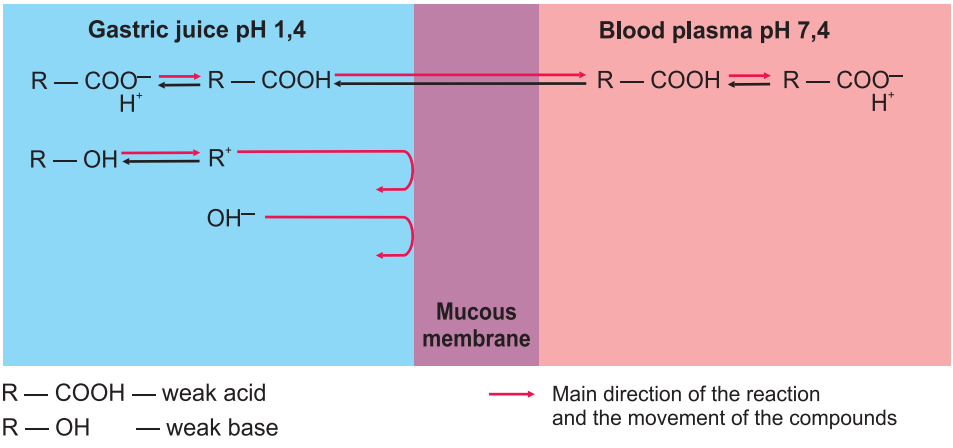

Fig. II.2. Importance of the pH of the medium for the absorption of substances from the stomach.

There are several known absorption mechanisms (Fig. II.3).

Passive diffusion occurs via the cellular membrane. It is defined by the concentration gradient of the compound. Lipophilic substances (mainly nonpolar) are easily absorbed via this route. The higher the lipophility of substances, the easier they penetrate through the cell membrane.

Facilitated diffusion. This involves transport systems functioning without energy consumption.

Filtration through the membrane pores. The diameter of the membrane pores in the intestinal epithelium is small (approximately 0.4 nm[3]). This is why water, certain ions and fine hydrophilic molecules (for example, urea) diffuse through them.

Active transport is the process that involves the transport systems of cell membranes. It has the following characteristics: selectivity to certain compounds, the possibility that two compounds compete for one transport mechanism, saturability (in high concentrations), ability of transport against concentration gradient and energy consumption (metabolic poisons inhibit active transport). Active transport provides absorption of hydrophilic polar molecules, a number of inorganic ions, sugars, amino acids and pyrimidines.

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[1] From Latin *ab* – away from, *sorbere* — to suck.

[2] In gastric acid medium these components are mainly present in unionized (lipophilic) form and are absorbed by diffusion.

[3] 1 nm (nanometer) = 1×10^{-9} m.

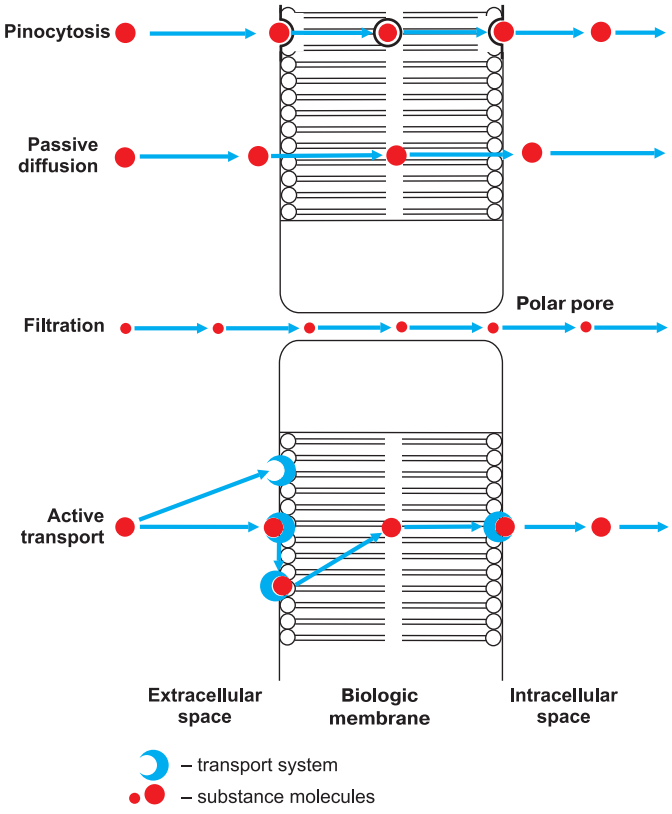


Fig. II.3. Main routes of substance absorption.

In pinocytosis[1] compounds are transported via endocytosis followed by vesicle formation (vacuole). The latter is filled with fluid and large molecules of transported substances. This vesicle migrates via the cytoplasm to the opposite side of the cell, where by means of exocytosis the vesicle content is expelled from the cell.

The above mentioned mechanisms of transport of substances through membranes are universal and play a role not only in the absorption but also in the distribution and excretion of various compounds.

The main mechanism of drug absorption in the small intestine is passive diffusion. A certain role is also played by the active transport. Absorption of a number of proteins and cyanocobalamin (vitamin B_{12}) in complex with Castle intrinsic factor appears to occur by active transport. Filtration through the cell membrane pores does not actually have any significance.

Absorption from the small intestine is relatively slow. It depends on the functional conditions of the intestinal mucous membrane, its motility and pH medium and quantity and quality of the intestinal contents. One should remember that from the small intestine, substances get into the liver (where a part of them is inactivated or excreted with bile) and only after that — into the general circulation. It has to be taken into account that some substances are not effective after oral administration because they are broken down under the influence of gastro-intestinal tract enzymes (for example, insulin) as

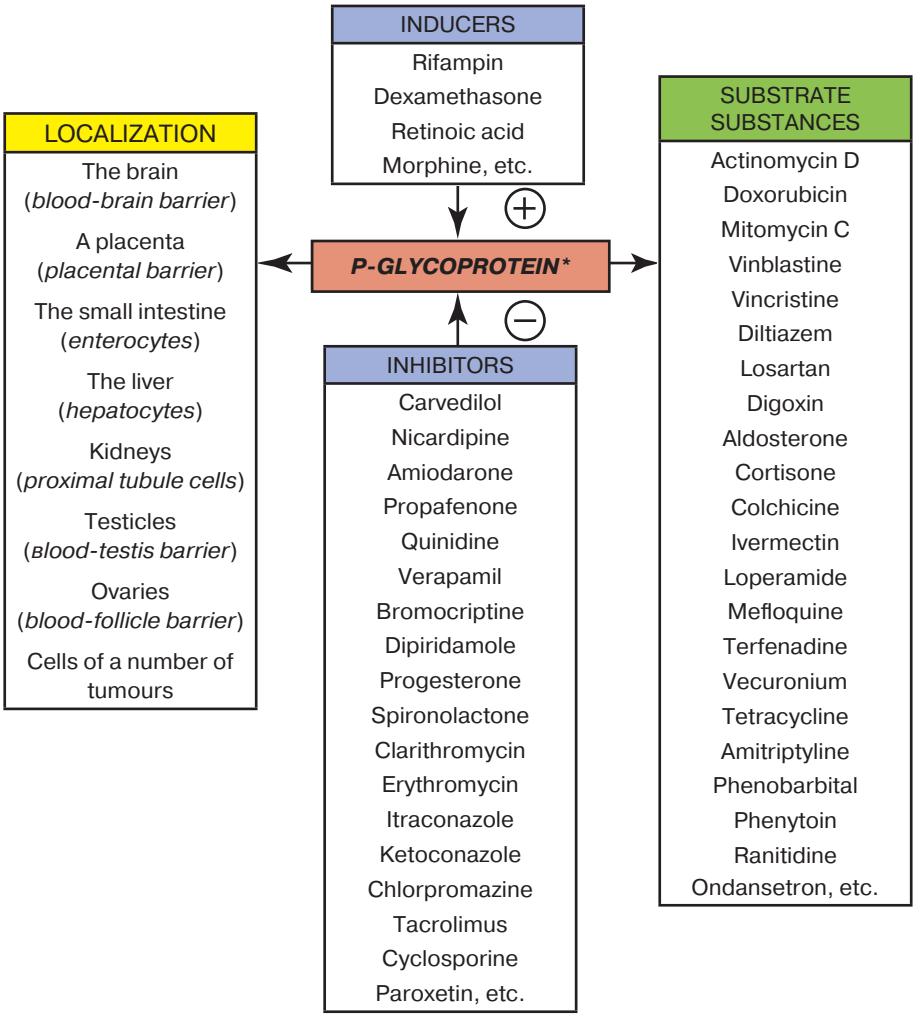
[1] From Greek *pine* — to drink.

well as under certain conditions of the medium, especially acid medium of the stomach (for example, benzylpenicillin).

If a drug can be broken down by gastric juice or has irritant action on the gastric mucosa, it is administered as a special formulation (capsules, dragee) that dissolve only in the small intestine.

An important role in providing active transport of substances through cell membranes, including their absorption, is played by membrane transporter P-glycoprotein[1], production of which is regulated by a special gene.

P-glycoprotein is located in the small intestine, liver, kidneys, histo-hematic barriers, pancreas, adrenal cortex, some hematopoietic and immunocompetent cells, and also in the number of tumour cells (Scheme II.1).



* Synonym: Multi-Drug Resistance Transporter 1 (MDR-1).

Scheme II.1. Some characteristics of P-glycoprotein.

[1] P — from *permeability* (Eng.).

The main function of P-glycoprotein transporter is to excrete drugs and other xenobiotics from cells (efflux[1] transporter).

P-glycoprotein participates in regulation of absorption, distribution, and excretion of many substances and ultimately has an impact on their effectiveness and toxicity. Essentially P-glycoprotein is a functional barrier of protecting organism cells against accumulation of toxic substances and helps to eliminate of xenobiotics and their metabolites from the body via the urine, the bile, the intestine. For example, P-glycoprotein located in an enterocytes of the small intestine is limiting absorption of a number of substances (digoxin, paclitaxel et al.) decreasing in such a way their bioavailability.

P-glycoprotein of blood-brain barrier prevents accumulation of many drugs (vinblastine, cyclosporin A, antraciclynes, etc.) in the brain by their active excretion into blood.

Of particular interest is the increased production of P-glycoprotein by a number of tumour cells, which is obviously one of the causes of development of resistance to effect of many antiblastomic drugs which are actively removed by this transporter from tumour cells.

In addition to P-glycoprotein substrates substances, drugs being inhibitors or inducers of it are known (see Scheme II.1). These substances can be used for improvement of basic treatment effectiveness, changing activity of P-glycoprotein: for example, in case of inhibition of tumour cell P-glycoprotein development, their resistance to anti-tumour drugs is suppressed.

Inhibition of P-glycoprotein of blood-brain barrier can be used for increasing concentration of many drugs substances in the brain.

Inhibitors and inducers of P-glycoprotein play an important role in drug interactions. So, P-glycoprotein inhibition of intestine, liver, and kidneys (for example by verapamil) significantly increases concentration of digoxin in blood plasma, accordingly, rifampicine, the inducer of P-glycoprotein is decreasing concentration of digoxin.

Due to the fact that the systemic effect of a substance develops only after its entrance into the bloodstream from which it moves to the tissues, the term «*bioavailability*» is suggested. It shows what proportion of the initial drug dose reached blood plasma intact. After oral administration bioavailability depends on the substance losses during its absorption from the gastro-intestinal tract and its first passage through the hepatic barrier. In bioavailability assessment, the area under the curve (AUC) is usually measured. It demonstrates the association between substance concentration in blood plasma and time (Fig. II.4) because this value is directly proportional to the amount of substance that entered systemic circulation. The other pa-

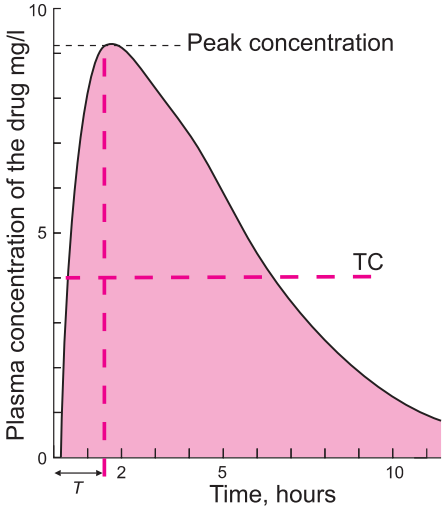


Fig. II.4. Determination of bioavailability after enteral administration
T — time to peak concentration of the drug.
TC – therapeutic concentration.
N o t e. Area under the concentration curve (AUC) for a certain period of time is measured.

[1] Efflux (Eng.) — expiration.

rameters are: maximal concentration of free (active) substance in blood plasma and the time necessary to achieve it. Bioavailability of a substance, administered intravenously, is considered to be 100%. Bioavailability can also be evaluated by measuring drug excretion with urine if it has not undergone biotransformation. In certain cases bioavailability can be measured by the extent of the pharmacological effect, if it is possible to measure it accurately.

If the drug is administered under the tongue — sublingual administration (in pills, granules, drops) — absorption starts quite quickly. In this case drugs have systemic action, bypassing the hepatic barrier in the first-pass and not interacting with enzymes and gastrointestinal tract medium. Certain highly active drugs used in small doses are administered sublingually (certain hormonal drugs, nitroglycerin).

Sometimes drugs are administered through the duodenal tube (for example, magnesium sulphate as cholagogue), which allows the creation of high compound concentration in the intestine.

After rectal administration (*per rectum*) a substantial part of the drug (about 50%) gets into the bloodstream, bypassing the liver. Besides, in this route of administration digestive enzymes do not affect the drug. Absorption from the rectum occurs by means of simple diffusion. Drugs are administered rectally as suppositories or medicinal enema (volume of 50 ml). If drugs have irritant action, they are combined with mucilage.

Drugs that have a protein, fat and polysaccharide structure are not absorbed in the large intestine.

Rectal administration is used also for local effect.

Parenteral administration routes comprise subcutaneous, intramuscular, intravenous, intra-arterial, intrasternal, intraperitoneal, inhalation, subarachnoid, suboccipital and some others.

Among parenteral routes the most common are subcutaneous, intramuscular and intravenous. The effect is especially quick after intravenous administration and a bit slower after intramuscular and subcutaneous administrations. To prolong the pharmacological effect, drugs are administered into the muscle as poorly soluble preparations (suspension) in oil and other bases, delaying absorption from the site of administration.

Intramuscular and subcutaneous routes of administration are not to be used for drugs that have marked irritant action, because it may be the cause of inflammatory reaction, infiltration and even necrosis.

Intravenous drugs are usually injected slowly. They may be given as a single dose, intermittent dosing, drip and infusion. The intravenous route is not acceptable for insoluble compounds, oil solutions (risk of embolism), drugs with marked irritant action (which may cause thrombosis and thrombophlebitis) and drugs inducing blood coagulation or hemolysis.

The disadvantages of the three abovementioned routes of administration are their relative complexity, as well as painfulness. The drugs have to be sterile, and medical staff have to be involved.

Intra-arterial administration allows to obtain high drug concentration in the area supplied by the selected artery. This route is sometimes used to inject antitumor drugs. To reduce general toxic effect of the drug, blood outflow may be artificially hindered

(by cross-clamping of the veins). Intra-arterial route is also used to give X-ray-opaque drugs, which help accurately define tumor, clot and vasoconstriction, or localize aneurism.

The intrasternal administration route (into the breastbone) is usually used in case of technical impossibility of intravenous injection (in children and elderly).

The intraperitoneal route of drug administration is rarely used (for example, antibiotics during abdominal operations).

Sometimes drugs are administered by the intrapleural route (into the pleural cavity).

For gaseous and volatile compounds the inhalation route of administration is the main one. The same route is used for some aerosols. The lungs present an extensive absorption area (90–100 m^2) with rich blood supply, and that is why absorption of the inhaled drugs occurs readily. The magnitude of effect is easily controlled by changing drug concentration in the inhaled gas. Absorption rate also depends on breathing volume, active surface of alveoli and their permeability, solubility of drugs in the blood and blood flow rate.

Drugs penetrate poorly through the blood-brain barrier can be administered under the arachnoid membrane (subarachnoidally, subdurally or suboccipitally). For example, some antibiotics can be given this way to treat infectious lesions of tissues and arachnoid membranes. The subarachnoid route of administration is used to introduce local anesthetics to perform spinal anesthesia.

Some drugs, usually highly lipophilic ones, are absorbed after skin application and have resorptive effects (for example, nitroglycerin). Transdermal drug preparations are becoming more widely used, since they help to maintain stable drug concentration in plasma over a long period of time.

Ionophoresis (diaelectrophoresis) route is sometimes used to administer ionized drugs (from skin or mucous membranes). Their absorption is caused by a weak electric field.

Certain drugs are administered intranasally (for example, adiurecrine). In this case absorption occurs from the nasal mucous membrane.

2. DRUG DISTRIBUTION IN THE BODY. BIOLOGICAL BARRIERS. STORAGE

After absorption, drugs enter the blood, then different organs and tissues. The majority of drugs are distributed unevenly, and only a small number of drugs distributes rather evenly (for example, some general anesthetics). Biologic barriers, that are encountered during drug distribution in the body, substantially influence the distribution: capillary wall, cell (plasma) membranes, blood-brain and placental barriers.

Most of the drugs go through the capillary wall easily, since it is a porous membrane (human pores average 2 nm in diameter). The exception is plasma proteins and their drug complexes. Hydrophilic (water-soluble) compounds pass through capillary wall intercellular clefts and enter interstitial space. There is barely any diffusion through the protein-phospholipid cellular membranes (they can get inside the cells only with transport systems' involvement). Lipophilic compounds penetrate well through capillary endothelium and cell membranes (Fig. II.5).

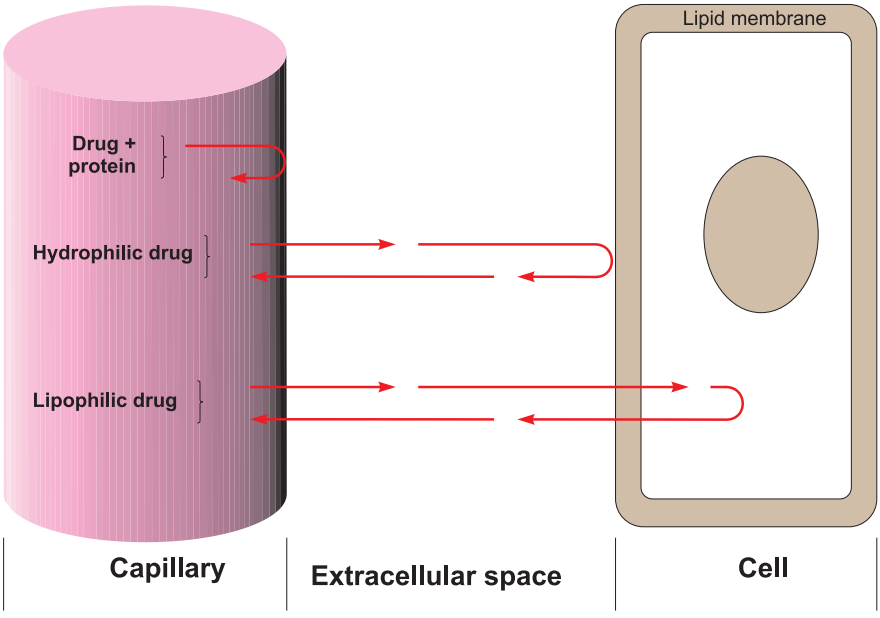


Fig. II.5. Factors influencing drug distribution.

The passage of a lot of drugs through the *blood-brain barrier*[1] is hindered. This is due to the characteristics of cerebral capillaries' structure (Fig. II.6). First of all, unlike the endothelium of periferal capillaries, their endothelium does not have intercellular clefts through which substances can penetrate well. In cerebral capillaries pinocytosis is actually absent. Glial elements (astroglia) line the external surface of the endothelium and, clearly, play the role of an additional lipid membrane. Polar compounds penetrate through the blood-brain barrier poorly. Lipophilic molecules easily pass through to the cerebral tissues. In general, drugs pass through the blood-brain barrier by means of diffusion, and some compounds — due to active transport. In certain small areas of the brain (epiphysis, neurohypophysis, medulla oblongata, and so on) there is almost no blood-brain barrier. It also has to be taken into account, that in some pathologic conditions (for example, in meningitis) the blood-brain barrier permeability is increased.

The passage of drugs through the blood-brain barrier is also controlled by P-glycoprotein transporter. It assists drugs' elimination from cerebral tissue into the blood, as well as hinders penetration of a number of compounds from blood into the CNS.

The placental barrier is a complex biological barrier. Lipophilic compounds pass through it by means of diffusion. Ionized polar drugs (for example, quaternary ammonium salts) penetrate poorly through the placenta. The placenta also has P-glycoprotein transporter.

To a certain extent drug distribution depends on the affinity of the drugs to certain tissues. Intensity of organ or tissue blood supply is also rather significant. It has to be taken into account that considerable amount of drugs may accumulate along their elimination paths. Drugs, that circulate in the body, partially bind to other molecules and form extra-

[1] There are three barriers in CNS, which limits the transport of compounds to the brain tissues:
1. Blood-brain barrier (BBB) – in the capillares in the brain.
2. Blood-cerebrospinal-fluid barrier (BCSFB) — choroid plexus in the ventricles.
3. Ependyma – epithelial layer covering the brain tissue.

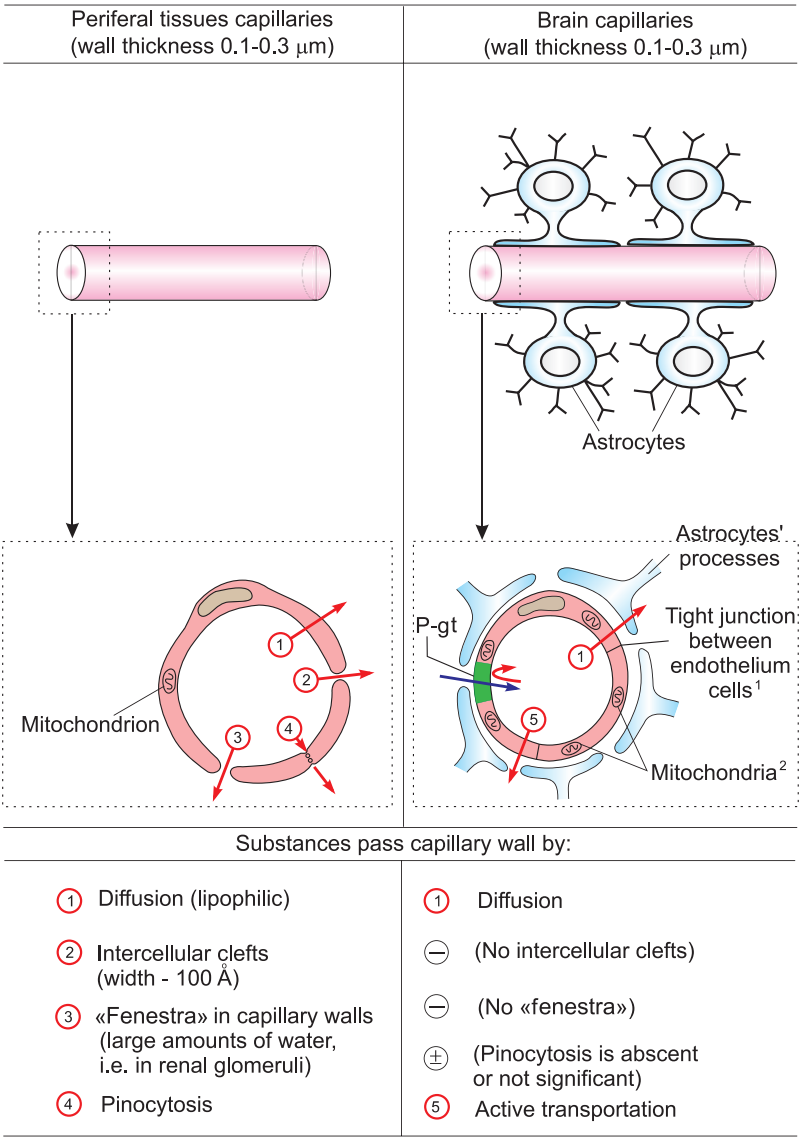


Fig. II.6. Principles of drug passage through capillaries of two types.
[1] Function as a solid membrane.
[2] Five times more than in usual capillaries.
P-gt — P-glycoprotein transporter.
Bleu arrow — direction of compounds flow under the influence of P-gt.

cellular and cellular depots. Plasma proteins can be referred to as extracellular depots (especially albumins). Many drugs bind with them rather significantly (more than by 90%).

Drugs may be accumulated in the connective tissue (some polar compounds, including quaternary ammonium salts) and bone tissue (tetracyclines).

Some drugs (particularly mepacrine) are found in cellular depots in especially large amounts. In the cells they bind to proteins, nucleoproteins and phospholipids.

Fat depots are of a particular interest, since lipophilic compounds may be retained in them (for example, some general anesthetics).

Drugs are deposited, as a rule, by means of reversible bonds. The duration of their presence in tissue depots varies widely. Thus, some sulfanilamides (sulfadimethoxine, other) form stable complexes with plasma proteins, and this partly explains the significant duration of their action. Heavy metal ions are retained in the body for a very long period.

It has to be taken into account that distribution of drugs, as a rule, does not indicate direction of their action. The latter depends on the sensitivity of tissues, i.e. on the affinity of the drug to biologic substrates, which define specificity of their action.

Clinical pharmacology often refers to the *apparent volume* of *distribution*[1] — V_d. It shows presumed volume of liquid in which a drug can be distributed (assuming that drug concentrations in plasma and other liquid media of the body is equal).

$$V_d = \frac{\text{Total amount of drug in the body}}{\text{Drug concentration in plasma}}.$$

The distribution volume demonstrates the drug fraction present in blood plasma. Lipophilic compounds that penetrate easily through tissue barriers and have wide distribution (plasma, interstitial fluid, intra-cellular fluid[2]) have high value of V_d. If the drug is only circulating in the blood, V_d values are low. This parameter is important for rational drug dosing, as well as for definition of elimination rate constant (K_{elim}) and drug half-life ($t_{1/2}$).

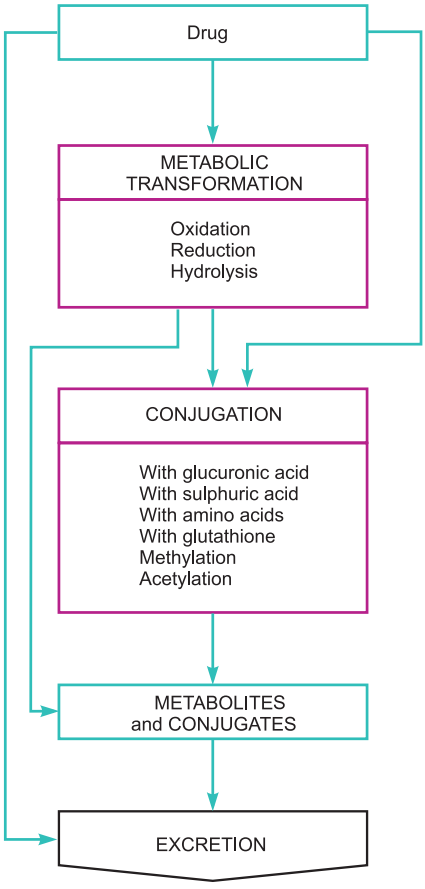


Fig. II.7. Ways of drug biotransformation.

3. BIOTRANSFORMATION OF DRUGS IN THE BODY

Most drugs undergo biotransformation in the body (Fig II.7). High-hydrophilic ionized compounds are usually eliminated unchanged. The exception among lipophilic substances are inhalation anesthetic drugs, most of which are not involved in chemical reactions occurring in the body. They are eliminated via the lungs in the same form as they had been administered. Most enzymes participate in drug biotransformation, and the most important among them are microsomal enzymes of the liver (located in the endoplasmic reticulum). They metabolize foreign lipophilic compounds (of different structure), transforming them into more hyd-

[1] Word *«apparent»* is used because the body can be viewed, for simplicity, as a single whole space (*one-compartment model*).

[2] In a human weighing 70 kg plasma consists of 3 l of water. Total amount of extracellular liquid is 12–15 l and total amount of water is 41 l.

rophilic. They do not have substrate specificity. Non-microsomal enzymes of various localizations (liver, intestine and other tissues, as well as plasma) are of very high significance, especially for the biotransformation of hydrophilic substances.

There are two main types of drugs bio-transformation: 1) metabolic transformation (I phase) and 2) conjugation (II phase). *Metabolic transformation* is a transformation occurring through oxidation, reduction and hydrolysis. For example, imipramine, ephedrine, chlorpromazine, histamine and codeine undergo oxidation. Oxidation occurs mostly due to microsomal oxidases of mixed action with participation of nicotinamide adenine dinucleotide phosphate (NADP), oxygen and P-450 cytochrome. Certain drugs undergo reduction, such as chloral hydrate, chloramphenicol, nitrazepam, etc. It occurs under the effect of nitro- and azoreductases and other enzymes. Esters (procaine, atropine, acetylcholine, suxamethonium, acetylsalicylic acid) and amides (procainamide) are hydrolyzed under the impact of esterases, carboxylesterases, amidases, phosphatases, etc. There are following examples to illustrate it (Fig. II.8).

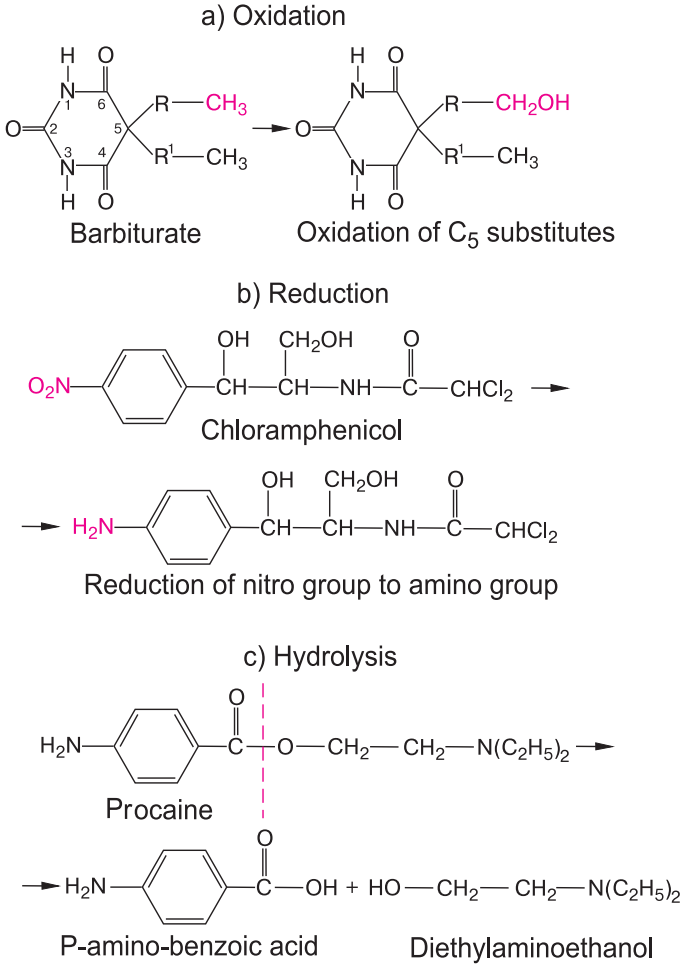


Fig. II.8. Metabolic transformation of drugs.

Conjugation is a biosynthetic process of binding of a number of chemical groups or molecules of endogenous compounds to the drug or its metabolites. The examples are: methylation (histamine, catecholamines), acetylation (sulfonamides), glucuronization (morphine, oxazepam) are binding with sulphates (chloramphenicol, phenol) or glutathione (paracetamol).

Many enzymes participate in the conjugation processes: glucoronil transferase, sulfotransferase, transacylase, methyltransferase, glutathione-S-transferase, etc.

Conjugation may be the only route of a drugs biotransformation or it may follow other routes of preceding metabolic transformation (see Fig. II.8). Examples of conjugates' formation (Fig. II.9).

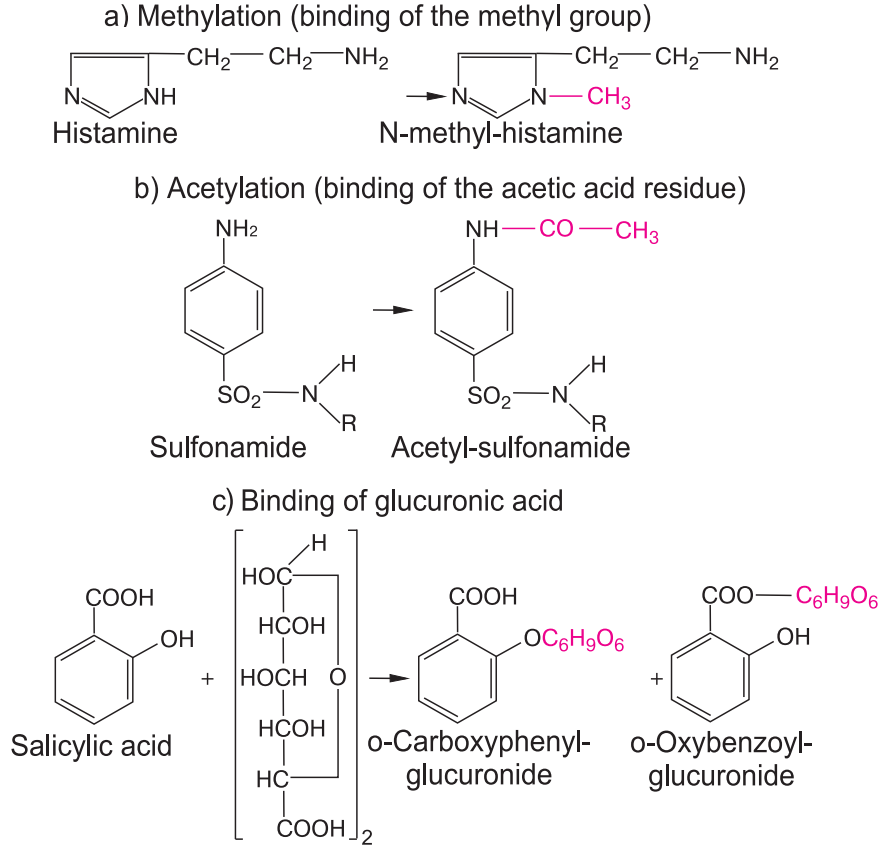


Fig. II.9. Conjugation of drugs.

In metabolic transformation and conjugation substances convert to more polar and more water-soluble metabolites and conjugates. It favours their further chemical transformations, if needed, as well as their excretion from the body. Kidneys are known to excrete hydrophilic compounds, while lipophilic ones undergo reabsorption in the renal tubules (Fig. II.10).

After metabolic transformation and conjugation drugs usually loose their biologic activity. Thus, these processes limit drug activity over time. In liver pathology associated with the reduction of activity of microsomal enzymes, duration of effect of some drugs increases. There are inhibitors of different enzymes, such as microsomal (chloramphenicol, phenylbutazone)

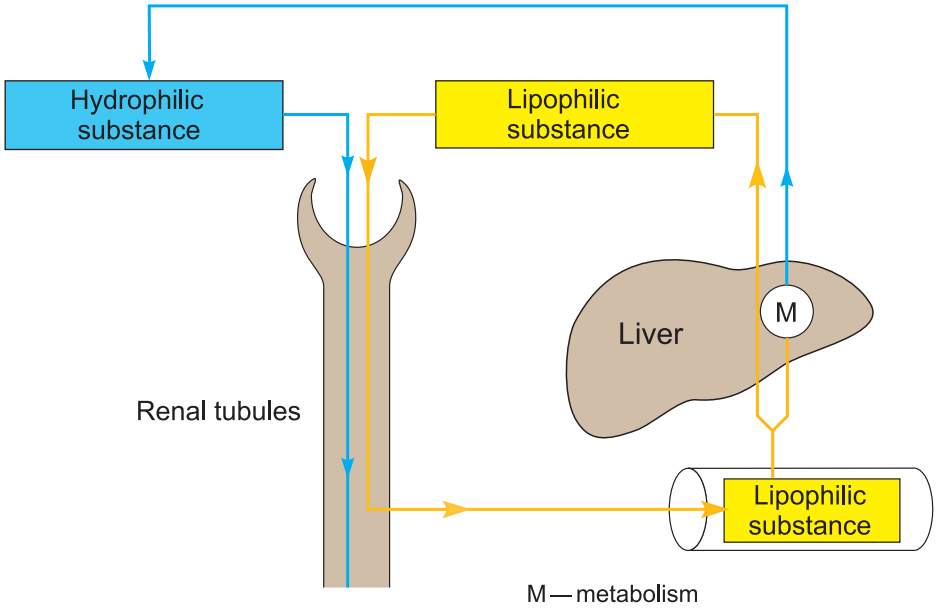


Fig. II.10. Excretion of hydrophilic and lipophilic substances.

and non-microsomal (anticholinesterase drugs, MAO inhibitors, etc.). They prolong the effect of drugs that are inactivated by these enzymes. In addition, there are compounds (for example, phenobarbital), which increase (induce) microsomal enzymes synthesis rate.

In some cases chemical transformations of the drugs in the body may lead to an increase in the resultant compound's activity (imipramine <desipramine) or toxicity (phenacetin <phenetidin). It may also change the mechanism of action (isoniazid which has antituberculous activity is one of the metabolites of the antidepressant iprazide), as well as transform one active compound into another (codeine partially converts into morphine).

4. ROUTES OF DRUG ELIMINATION FROM THE BODY

Drugs, their metabolites and conjugates are mainly eliminated with urine and bile.

In the kidneys low-molecular compounds, dissolved in plasma (not bound to proteins), are filtered through membranes of glomerular capillaries and glomerular capsules (Fig. II.11 and II.12). Besides, active secretion of substances in proximal tubules with the participation of the transport systems is essential. This is the elimination route of organic acids and bases, penicillins, salicylates, sulfonamides, quinine, histamine, thiazides, etc. Some lipophilic compounds can penetrate from blood into tubular lumen (proximal and distal) by simple diffusion through their walls.

The elimination of substances greatly depends on their reabsorption in renal tubules. Drugs are reabsorbed mainly by simple diffusion. This mainly concerns lipophilic non-polar compounds, easily penetrating through biologic membranes. Polar compounds are poorly reabsorbed from the renal tubules. That is why elimination of weak acids and bases greatly depends on urine pH. Thus, when urine pH is alkaline, there is an increase in the elimination of acidic compounds (for example, salicylic acid, phenobarbital). When urine pH is

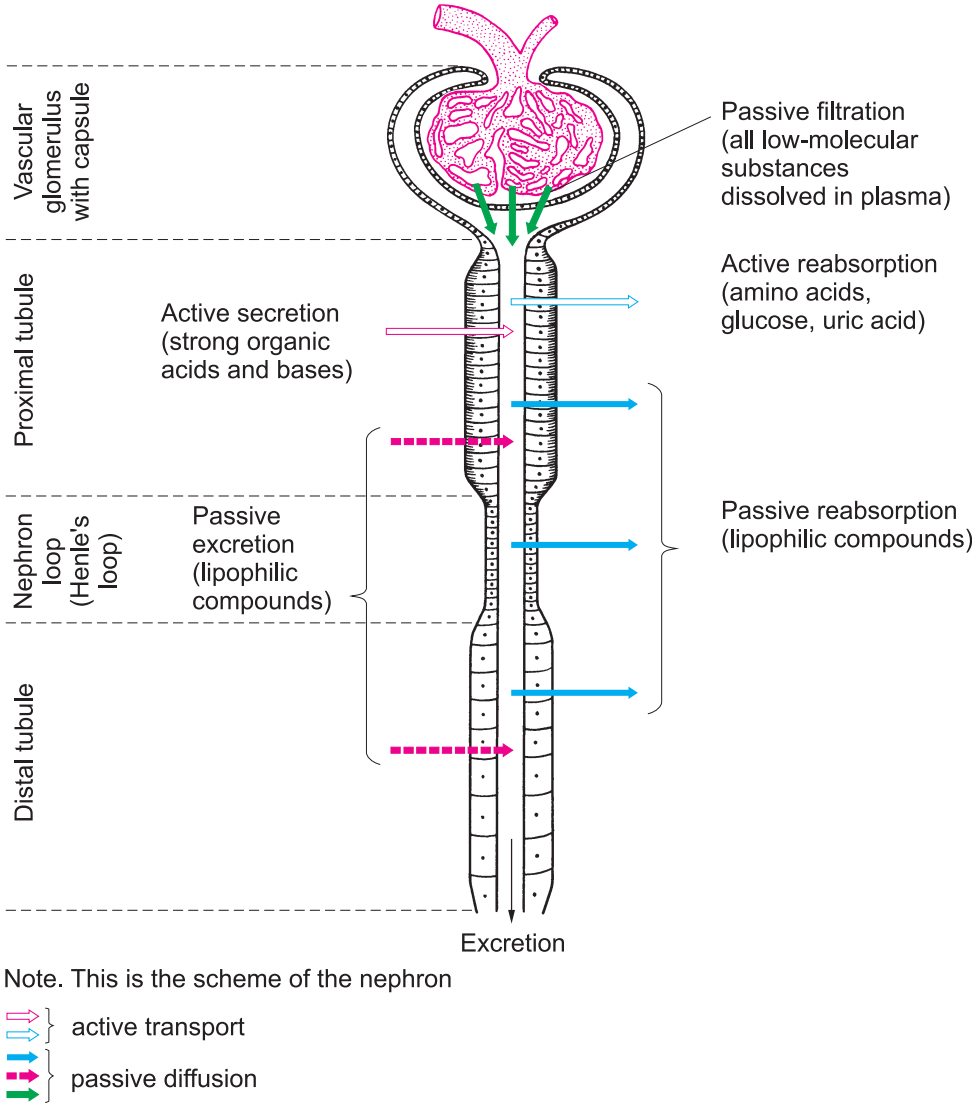


Fig. II.11. Basic processes affecting renal excretion of pharmacological substances.

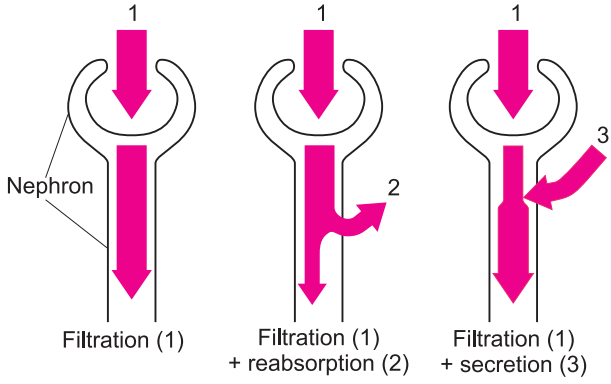


Fig. II.12. Principles of renal excretion.

acidic, elimination of bases increases (imipramine, etc.). The reason for this is the ionization of the mentioned compounds which prevents their reabsorption from the renal tubules.

Active transport is involved in reabsorption of a number of endogenous substances (amino acids, glucose, uric acid).

Significant mechanisms of the elimination of a number of drugs (tetracyclines, penicillins, phenytoin, colchicine, other) and especially products of their transformation is their transfer with bile into the intestine. A certain proportion of the drug is then eliminated with faeces, and the rest is reabsorbed. The cycle continues on, with the compound then again being eliminated into the intestine and so on (so-called hepato-intestinal circulation or hepatic recirculation; Fig. II.13).

The lungs mainly eliminate gaseous and most volatile substances (for example, inhalation anesthetics).

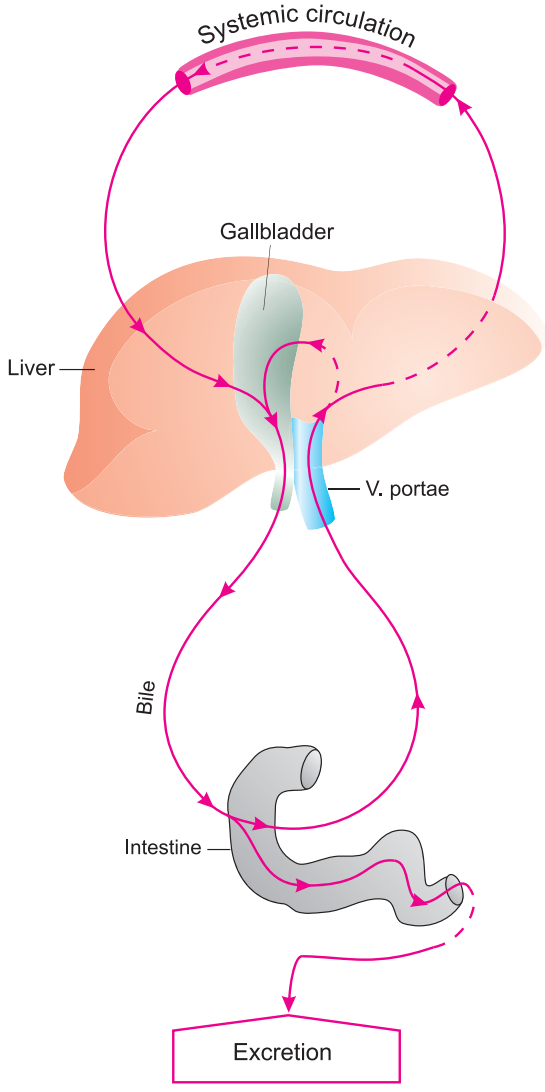


Fig. II.13. Hepato-intestinal circulation of substances.

Some drugs are eliminated by salivary glands (iodides), sweat glands (antileprotic ditophal), gastric (quinine, nicotine) and intestinal glands (weak organic acids) and lacrimal glands (rifampicin).

It has to be taken into account that during lactation a lot of substances taken by a nursing mother are eliminated via mammary glands (hypnotics, opioid analgesics, ethyl alcohol, nicotine, etc.). That is why one should be extremely cautious when administering drugs to a nursing mother. The drugs can get into the baby's body with breast milk and have unfavorable effects.

The elimination of drugs from the body occurs by excretion and biotransformation. A number of parameters are used as quantitative characteristics of elimination process: elimination rate constant (K_{elim}), «half-life» ($t_{1/2}$) and systemic clearance (Cl_T).

Elimination rate constant (K_{elim}) shows the rate of drug elimination from the body. It is defined according to the formula:

$$K_{elim} = \frac{0.693}{t_{1/2}}.$$

To define the rate of drug elimination from the body «*half-life*» (elimination half-life, $t_{1/2}$) parameter is also used. It shows the time necessary to decrease drug concentration in blood plasma by 50%:

$$t_{1/2} = \frac{0.693}{K_{elim}} = \frac{0.693 \cdot V_d}{Cl_T}$$

This parameter is used to adjust doses of drugs and intervals between the times of their administration in order to achieve stable drug concentration («steady state»). It is known that 90% of the drug is eliminated during the period that equals 4 $t_{1/2,}$ and this is considered in the dosing of the drugs. It also has to be considered that $t_{1/2}$ is defined not only by drug elimination from the body, but also by its biotransformation and storage.

Another parameter used as a quantitative characteristic of drug elimination rate is *clearance*[1] (Cl). This indicates the rate of removal of a substance from the blood (clearance) (it is measured as volume over time, or if necessary it can be expressed in relation to body mass or surface: ml/min, ml/kg/min, l/m^2/h, etc.). The parameters measured are: total (Cl_T), renal (Cl_R) and hepatic (Cl_H) clearance.

$$Cl_T = \frac{\text{Drug elimination rate}}{\text{Drug concentration in blood plasma}}.$$

Total clearance depends on such parameters as volume of distribution (V_d), «half-life» ($t_{1/2}$) and constant of elimination (K_{elim}).

$$Cl_T = V_d \cdot K_{elim} = \frac{V_d \cdot 0.693}{t_{½}}.$$

Renal clearance depends on the processes of filtration, secretion and reabsorption. It is possible to assess renal clearance by comparing drug concentration in urine and plasma (considering urine flow rate as well).

Hepatic clearance occurs via drug uptake and its further biotransformation by hepatocytes as well as drug secretion into the bile ducts.

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[1] From Latin *clarus* — clear.

5. LOCAL AND SYSTEMIC EFFECTS OF THE DRUGS. DIRECT AND REFLEX EFFECTS. LOCALIZATION AND MECHANISM OF ACTION. DRUG «TARGETS». REVERSIBLE AND IRREVERSIBLE ACTIONS. SELECTIVE ACTION

Drug effect that occurs at the site of its application is called local. For example, coating drugs cover the mucous membrane preventing irritation of the afferent nerve endings. In local anesthesia, application of a local anesthetic onto the mucous membrane leads to the blockade of sensory nerves endings only at the site of the drug application. However, truly selective local action is observed extremely rarely since most substances are either partially absorbed or have a reflex effect.

The effect of a drug that develops after it is absorbed and carried to the tissues by the blood flow, is called systemic (resorptive[1]). Systemic effect depends on the routes of administration of drugs and their ability to penetrate through biologic barriers.

Local and systemic effects of drugs can be either direct or reflex. The first occurs at the site of contact of the drug with the tissue. Reflex effect is produced when substances influence extero- or interoceptors causing changes in the status of either corresponding nerve centers or effector organs. For example, application of mustard plasters to treat respiratory illnesses reflexively improves their trophism (essentially mustard oil stimulates skin exteroceptors). Lobeline, administered intravenously, stimulates carotid glomerular chemoceptors and increases volume and frequency of respirations via reflex stimulation of the respiration center.

The main purpose of pharmacodynamics is to find out where and how the drug acts to cause its effects. Due to improvements in methodology these questions are answered not only on systemic or organ level, but also on cellular, subcellular, molecular and submolecular ones. Thus, for neurotropic drugs it is possible to distinguish the structures of the nervous system and the synapses that have the highest sensitivity to these compounds. One can localize tissue enzymes, cells and subcellular formations, activity of which changes most substantially due to substances affecting metabolism. In all cases the search is for biologic «targets» – the substrates with which the drug interacts.

Ion channels, enzymes, transport systems and genes serve as «targets» for drugs.

Receptors are active groups of substrates' macromolecules that a drug interacts with. Receptors that provide for the expression of the main effect of the drug are called specific.

There are four types of receptors (Fig. II.14).

I. Receptors directly controlling ion channel function. These are receptors coupled directly with ion channels (nicotinic cholinoceptors, $GABA_A$-receptors and glutamate receptors).

II. Receptors coupled with effector via the «G-proteins — second messengers» or «G-proteins — ion channels» systems. Such receptors exist for most hormones and neurotransmitters (muscarinic cholinoceptors, adrenoceptors).

III. Receptors directly controlling effector enzyme function. They are directly associated with tyrosine kinase and regulate phosphorylation of proteins. Insulin receptors and a number of growth factors function this way.

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[1] From Latin *resorbeo* — resorb.

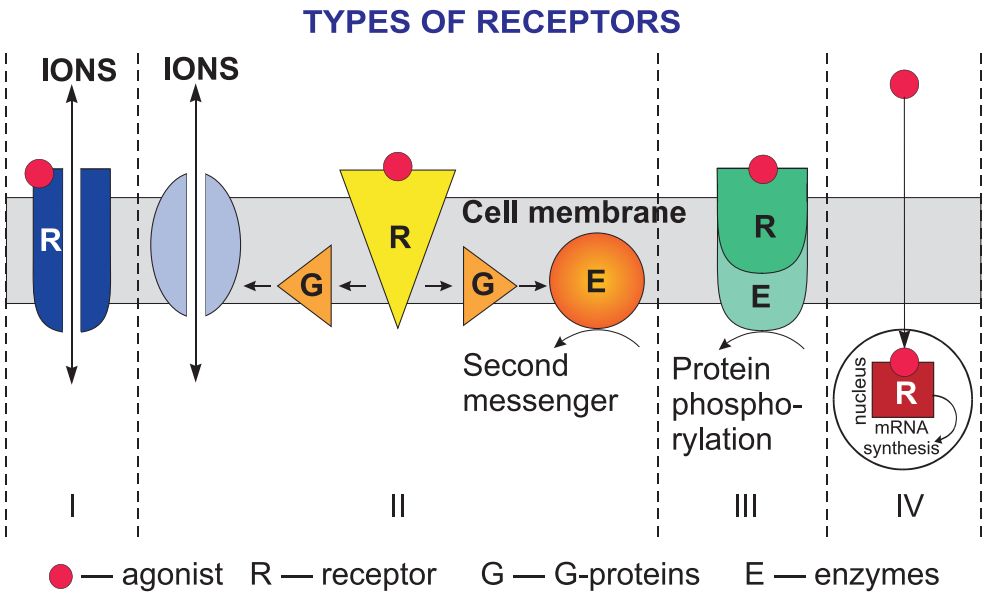

Fig. II.14. Principles of effects of agonists on processes controlled by receptors.
I — direct effect on ion channels permeability (nicotinic cholinoceptors, $GABA_A$-receptors); *II* — mediated effect (via G-proteins) on permeability of ion channels or enzymes controlling formation of second messengers activity (muscarinic cholinoceptors, adrenoceptors); *III* — direct influence on the activity of effector enzyme tyrosine kinase (insulin receptors, receptors of a number of growth factors); *IV* — effect on DNA transcription (steroid hormones, thyroid hormones).

IV. Receptors controlling DNA transcription are intracellular receptors (soluble cytosolic or nuclear proteins) unlike membrane receptors of types I–III. Steroid and thyroid hormones interact with this type of receptors.

Study of receptor subtypes (Table II.1) and associated effects proved to be useful. First studies on this subject deals with the synthesis of most β-adrenoblockers that are widely used in different diseases of the cardio-vascular system. Next came histamine H_2-receptors blockers that are effective treatments for stomach and duodenum ulcers. In subsequent years a lot of other drugs have been synthesized, which has affected different subtypes of α-adrenoceptors, dopamine and opioid receptors, etc. Investigations of these novel drugs played an important role in the formation of a new group of selectively acting drugs which are widely used in medical practice.

With regard to the effect of the drugs on postsynaptic receptors it has to be noted that drugs of both endogenous (for example, glycine) and exogenous origin can bind allosterically (for example, anxiolytics of benzodiazepine series; see Chapter 11.4. Fig. 11.7). Allosteric interaction[1] with receptors does not induce a «signal». However, modulation of basic neurotransmitter effect can both be intensified and weakened. The creation of drugs of this type opens new possibilities for regulation of the CNS function. A characteristic feature of the allosteric action neuromodulators is that they do not have a direct effect on the basic mediator transmission but only modify it in the appropriate direction.

[1] From Greek *allos* — different, *stereos* — solid shape.

Table II.1. Examples of some receptors and their subtypes.

Receptors for	Subtypes
Adenosine	A_1, A_{2A}, A_{2B}, A_3
α_1-Adrenoceptors	α_{1A}, α_{1B}, α_{1C}
α_2-Adrenoceptors	α_{2A}, α_{2B}, α_{2C}
β–Adrenoceptors	β_1, β_2, β_3
Angiotensin	AT_1, AT_2
Bradykinin	B_1, B_2
GABA	$GABA_A$, $GABA_B$, $GABA_C$
Histamine	H_1, H_2, H_3, H_4
Dopamine	D_1, D_2, D_3, D_4, D_5
Leukotriene	LTB_4, LTC_4, LTD_4
Muscarinic cholinoceptors	M_1, M_2, M_3, M_4
Nicotinic cholinoceptors	Muscular type, neuronal type
Opioid	μ, δ, κ
Prostanoids	DP, FP, IP, TP, EP_1, EP_2, EP_3
Purine	P_{2X}, P_{2Y}, P_{2Z}, P_{2T}, P_{2U}
Excitatory amino acids (ionotropic)	NMDA, AMPA, kainite receptors
Neuropeptide Y	Y_1, Y_2
Atrial natriuretic peptide	ANPA, ANPB
Serotonin	5-$HT_{1(A-F)}$, 5-$HT_{2(A-C)}$, 5-HT_3, 5-HT_4, 5-$HT_{5(A-B)}$, 5-HT_6, 5-HT_7
Cholecystokinin	CCK_A, CCK_B

The discovery of presynaptic receptors (Table II.2) played an important role in the understanding of the regulation of the mechanisms of synaptic transmission. It investigated the ways of homotropic autoregulation (effect of the released neurotransmitter on presynaptic receptors of the same nerve ending) and heterotropic regulation (presynaptic regulation via another neurotransmitter) of neurotransmitter release, which allowed to assess specificities of the action of the most substances in a new fashion. These data were used also for targeted search for some drugs (for example, prazosin).

The affinity of a substance to a receptor that leads to the formation of a «drug-receptor» complex is referred to as «affinity»[1]. The ability of a drug to stimulate a receptor during an interaction and to induce an effect is called intrinsic activity.

Drugs that cause a biologic effect by inducing changes in specific receptors during an interaction are called agonists (they have intrinsic activity). Stimulating action of an agonist on receptors can lead to activation or inhibition of cellular function. If an agonist, interacting with receptors, has a maximum effect, it is called a full agonist[2].

[1] From Latin *affinis* — related.
[2] From Greek *agon* — to struggle.

Table II.2. Examples of presynaptic control of neurotransmitter release by cholinergic and adrenergic endings.

Effect	Presynaptic receptors
Neurotransmitter release inhibition	M_2-cholinoceptors α_2-Adrenoceptors Serotonin 5-HT_1-receptors Purine P_1-receptors Prostaglandin receptors Histamine H_2-receptors Opioid δ-receptors Dopamine D_2-receptors
Neurotransmitter release stimulation	β_2-Adrenoceptors Angiotensin II AT_1-receptors

Unlike the latter, partial agonists do not cause maximum effect after interaction with the same receptors. Drugs that bind with receptors but do not cause their stimulation are called antagonists[1]. They do not have intrinsic activity (equals 0). Their pharmacological effects are determined by antagonism with endogenous ligands (mediators, hormones), as well as with exogenous drugs-agonists. If antagonists interact with the same receptors as agonists, they are called *competitive antagonists*. If antagonists interact with other sites of a macromolecule that are not linked to a specific receptor, but interrelated with it, they are called *noncompetitive antagonists*. When a drug acts as an agonist on one receptor subtype and as antagonist on another one, it is referred to as an agonist-antagonist. For example, analgesic pentazocine is μ-antagonist and agonist of δ- and κ-opioid receptors.

«Drug-receptor» interaction occurs via intermolecular bonds. One of the strongest bonds is a covalent one. It is seen in a limited number of drugs (α-adrenoblocker phenoxybenzamine, some antiblastomic drugs). Common ion bonds are less durable, they occur due to electrostatic bonding of drugs with receptors. The latter is typical for ganglionic blockers, neuromuscular blockers (curare-like drugs), acetylcholine. Van der Waals forces play an important role and are the base of hydrophobic interactions, as well as hydrogen bonds (Table II.3).

The durability of the «drug-receptor» bond determines whether the drug action is reversible (characteristic for most drugs) or irreversible (in case of covalent bond, as a rule).

If a drug interacts only with functionally univalent receptors of certain localization and does not affect other receptors, action of such a drug is referred to as selective. For example, some curare-like drugs block nicotinic cholinoceptors of the end-plate rather selectively, causing relaxation of skeletal muscles. In doses, producing myoparalytic action, they do not significantly affect other receptors.

The affinity of a drug for one particular receptor is the basis of action selectivity. It depends on a drug and a receptor being complementary to each other, i.e. having adequate functional groups or structural organization. The term «selective action» is often replaced by the term «predominant action», because there is no real absolute selectivity of drugs.

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[1] From Greek *anti* — against, *agon* — to struggle.

Table II.3. Types of drug-receptor interaction.

Interaction types	Approximate bonding strength		Decrease of bonding strength depending on the distance between atoms (r)
	kcal/mol	kJ/mol	
Covalent	50–100	210–420	
Electrostatic bonding (ionic)	5	21	r^{-2}
Ion-dipole	2–5	8–21	r^{-3}
Dipole-dipole	1–3	4–12	r^{-4}
Hydrogen bond	2–5	8–21	r^{-4}
Van der Waals (dispersionic)	0.5	2	r^{-7}
Hydrophobic[1]	*		

[1] Interaction of nonpolar molecules in the water.

* 0.7 kcal (3 kJ) over one CH_2-group.

To assess the interaction of the drugs with membrane receptors and transmission signals from the external surface of membrane to the internal one, one has to consider intermediate links that connect receptor and effector. The most important components of this system are G-proteins[1], enzyme group (adenylyl cyclase, guanylyl cyclase, phospholipase C) and second messengers [cyclic adenosine monophosphate — cAMP), cGMP (cyclic guanosine monophosphate), IP_3 (inositol triphosphate) and DAG (diacylglycerol), Ca^{2+}]. An increase in the second messengers' formation leads to the activation of protein kinases that provide intracellular phosphorylation of important functional proteins and development of various effects.

Most steps of this complex cascade may be a target of an effect of a pharmacological substance. However, for the moment such instances are rather limited. Thus, only toxins are known to bind with G-proteins. Comma bacillus toxin interacts with G_s-protein, and pertussis bacillus toxin interacts with G_i-protein.

Some drugs have direct effects on enzymes participating in regulation of biosynthesis of second messengers. Thus, the plant diterpene forskoline, used in experimental trials, stimulates adenylyl cyclase (direct action). Phosphodiesterase is inhibited by methylxanthines. In both cases concentration of cAMP inside the cell increases as a result of a pharmacological action.

One of the important «targets» for drugs' action are **ion channels.** Progress in this field is mostly associated with the development of methods for recording the functions of separate ion channels. It has stimulated not only fundamental research, devoted to the study of ion kinetics, but also favoured creation of new drugs that control ion flows (Table II.4).

In the middle of XX century it was found that local anesthetics block voctage-gated Na^+-channels. Most antiarrhythmic drugs are Na^+-channel blockers. Besides it was shown that a number of antiepileptic drugs (phenytoin, carbamazepine) also

[1] Types of some G-proteins and their functions: G_s — coupling of excitatory receptors with adenylyl cyclase; G_i — coupling of inhibitory receptors with adenylyl cyclase; G_o — coupling of receptors with ion channels (Ca^{2+} flow decreases); G_q coupling of receptors that activate phospholipase C; G proteins consist of 3 subunits — α, β and γ.

Table II.4. Drugs affecting ion channels.

LIGANDS OF Na^+-CHANNELS	LIGANDS OF Ca^{2+}-CHANNELS	LIGANDS OF K^+-CHANNELS
Na^+-channels blockers Local anesthetics (procaine, lidocaine) Antiarrhythmic drugs (quinidine, procainamide) Antiepileptic drugs (phenytoin, carbamazepine) **Activators of Na^+-channels** Veratridine (alkaloid; hypotensive drug)	**Ca^{2+}-channels blockers** Antianginal, antiarrhythmic and antihypertensive drugs (verapamil, nifedepine, diltiazem) **Activators of Ca^{2+}-channels** Bay K 8644 (dihydropyridine; cardiotonic and vasoconstrictor action)	**K^+-channels blockers** Antiarrhythmic drugs (amiodarone) Drug facilitating neuromuscular transmission (pimadin) Antidiabetic drug (glibenclamide) **Activators of K^+-channels** Antihypertensive drugs (minoxidil) Antianginal drugs (nicorandil)

block voltage-gated Na^+-channels and their anticonvulsant activity may be associated with this effect.

In the last 30—40 years a lot of attention was paid to Ca^{2+}-channel blockers, preventing passage of Ca^{2+} inside a cell through voltage-gated Ca^{2+}-channels. Increased interest in this group of drugs is mostly associated with that Ca^{2+} are involved in most physiologic processes: muscular contraction, secretory activity of cells, neuromuscular transmission, platelet function, etc.

Most drugs of this group proved to be rather effective in management of such common diseases as angina pectors, cardiac arrhythmias and arterial hypertension. Such drugs as verapamil, diltiazem, nifedepine and many others are widely recognized.

Activators of Ca^{2+}-channels have also attracted attention, for example, dihydropyridine derivatives. Such drugs can be used as cardiotonics, vasoconstrictors, drugs stimulating hormone and neurotransmitters release as well as CNS stimulators.

The search for blockers and activators of Ca^{2+}-channels with predominant effect on the heart and blood vessels of different locations (brain, heart, other) and CNS is especially important. There are certain prerequisites for it, because Ca^{2+}-channels are heterogeneous.

In recent years a lot of attention has been paid to the drugs controlling function of K^+-channels. Potassium channels are shown to be very different in their functional characteristics. On one hand, it significantly complicates pharmacological studies, and on the other hand this creates actual prerequisites for the search of selective action drugs. There are both activators and blockers of potassium channels.

Activators of potassium channels aid their opening and cause outflux of K^+ from the cell. If it occurs in smooth muscles, membrane hyperpolarization develops and muscle tone decreases. This is a mechanism of action of minoxidil and diazoxide, used as hypotensive drugs, as well as antianginal drug nicorandil.

Potassium channel blockers include also antiarrhythmic drugs (amiodarone, ornid, sotalol).

Blockers of ATP-dependant potassium channels in the pancreas increase insulin secretion. This is the mechanism underlying the effect of the antidiabetic drugs of sulfonylurea group (chlorpropamide, etc.).

The stimulating effect of aminopyridines on CNS and neuromuscular transmission is also related to their blocking effect of potassium channels.

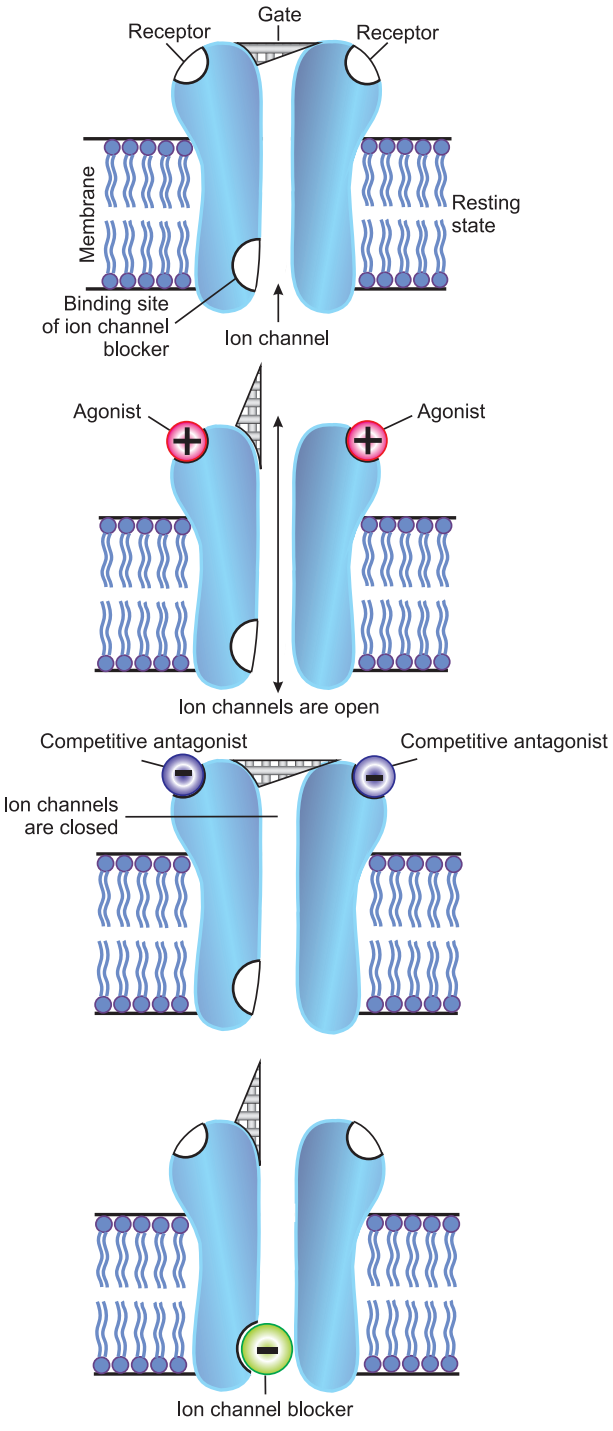

Fig. II.15. Possible sites of binding of agonists, antagonists and ion channel blockers.

Thus, the effect on ion channels underlies the action of different drugs.

Enzymes are an important "target" for drug action. The possible effect on enzymes, controlling formation of second messengers (for example, cAMP), has already been

mentioned. The mechanism of action of non-steroid anti-inflammatory drugs is the inhibition of cyclooxygenase and decrease of prostaglandin biosynthesis. One group of antihypertensive drugs inhibit angiotensin converting enzyme (captopril, etc.). Anticholinesterase drugs block acetylcholinesterase and stabilize acetylcholine.

Methotrexate — antiblastomic drug (antagonist of folic acid) blocks dihydrofolate reductase, preventing formation of tetrahydrofolate, which is necessary for the synthesis of purine nucleotide timidilate. Antiherpetic drug acyclovir that transforms into acyclovirtriphosphate, inhibits viral DNA-polymerase.

One more possible «target» of drugs action is **transport systems** for polar molecules, ions, and small hydrophilic molecules. They comprise so-called transport proteins that carry drugs through the cell membrane. They have sites that recognize endogenous substances. These sites may interact with drugs as well. Thus, tricyclic antidepressants block neuronal uptake of norepinephrine. Reserpine blocks storage of norepinephrine in vesicles. One of the significant achievements is the creation of the inhibitors of the proton pump in the mucous membrane of the stomach (omeprazole, etc.). These drugs showed high efficacy in the treatment of stomach and duodenal ulcer, as well as in hyperacid gastritis.

Since the sequencing of human genome, extensive studies are being carried out exploring the use of **genes** as a target. There is no doubt that gene therapy is one of the most important directions of contemporary and future pharmacology. The idea of this therapy is regulation of functions of those genes, the etiopathogenetic role of which has been proven. The main principles of gene therapy are to increase, decrease or stop gene expression, as well as to replace a mutant gene.

It has become possible to solve these problems due to the possibility of cloning chains with preset sequences of nucleotide. Introduction of such modified chains is meant to normalize synthesis of the proteins that determine this pathology, and therefore to restore cell function.

The central issue in successful development of gene therapy is the delivery of nucleic acids to target cells. Nucleic acids have to get from extracellular spaces to plasma, and then, having passed through cell membranes, penetrate into the nucleus and incorporate into chromosomes. It has been suggested to use some viruses as transporters or vectors (for example, retroviruses, adenoviruses). With the help of genetic engineering vector-viruses are deprived of the ability to replicate, i.e. they do not produce any new virions. Other transport systems have also been suggested, such as complexes of DNA with liposomes, proteins, plasmid DNA and other microparticles and microspheres.

Naturally, an incorporated gene should function for a rather longer period of time, i.e. gene expression should be stable.

Potential possibilities for the use of gene therapy include most hereditary diseases. They comprise immunodeficiency conditions, some types of hepatic pathology (including hemophilia), hemoglobinopathy, pulmonary diseases (for example, cystic fibrosis), muscle diseases (Duchenne's muscular dystrophy), etc.

A large number of studies are investigating potential ways to use gene therapy for the management of tumors. These possibilities include blocking the expression of oncogenic proteins; activation of genes that can inhibit tumor growth; stimulation of formation of special tumor enzymes that transform prodrugs into compounds that are toxic only for

tumor cells; increasing marrow cells' resistance to the inhibiting action of antiblastomic drugs; increasing immunity against cancer cells, etc.

In cases when it is necessary to block expression of certain genes, a special technique of so-called antisense oligonucleotides is used. The latter are relatively short chains of nucleotides (15–25 bases), which are complementary to the zone of nucleic acids where the target gene is located. As a result of the interaction with antisense oligonucleotide the expression of this gene is inhibited. This principle of action is interesting for the management of viral, oncological and other diseases. The first drug from the antisense oligonucleotides' group is vitravene (fomivirsene). It is applied locally in rhinitis caused by cytomegalovirus infection. Drugs for the treatment of myeloid leukemia and other diseases of blood have been synthesized recently. They are now in clinical trials.

At the moment the issue of using genes as targets for pharmacological effect is in the stage of fundamental studies. There are only very few perspective drugs of this kind that are in preclinical and clinical trials. However, there is no doubt that in this century many effective drugs for gene therapy of not only hereditary, but also acquired diseases will appear. These will be fundamentally new drugs to treat tumors, viral diseases, immunodeficiency conditions, hematosis and blood coagulation disturbances, atherosclerosis, etc.

Thus, possibilities for the targeted drugs effect are rather variable.

6. DEPENDENCE OF PHARMACOTHERAPEUTIC ACTION ON DRUG PROPERTIES AND PATTERN OF USE

A) Chemical structure, physical–chemical and physical properties of drugs

Drug properties depend on their chemical structure, presence of functionally active groups and shape and size of their molecules to a significant extent. The effective interaction of a drug with a receptor requires a structure that provides their closest contact. The strength of intermolecular bonds depends on the degree of drug-receptor proximity. Thus, it is known that in an ion bond the electrostatic attraction of two opposite charges are in inverse proportion to the squared distance between them, and Van der Waals forces are in an inverse proportion to 6–7th power of distance (see Table II.3).

The spatial relationship of a drug with a receptor, i.e. complementarity, is especially important for their interaction. It is confirmed by differences in the activity of stereoisomers. Thus, D(+)-epinephrine substantially yields in activity to L(–)-epinephrine in its effect on arterial pressure. These compounds are distinguished by the spatial relationship of molecular structural elements that have a key significance for their interaction with adrenoceptors.

If a drug has several functionally active groupings it is necessary to take into account the distance between them. Thus, in the series of bis-quaternary ammonium compounds $(CH_3)_3N^+–(CH_2)_n–N^+(CH_3)_3 \cdot 2X^-$ for ganglion blocking action n=6 is optimal, while n=10 and 18 are optimal for neuromuscular block. It indicates a definite distance between anionic structures of nicotinic cholinoceptors with which ion bonding of quater-

nary nitrogen atoms occurs. Other important factors for such compounds are radicals, «screening» cation centers, the size of positive atom and charge concentration, as well as the structure of the molecule that connects cation groupings.

Elucidation of dependence between chemical structure of substances and their biologic activity is one of the most important directions in creating new drugs. Besides, comparison of optimal structures of different chemical groups with similar mechanism of action allows us to formulate an understanding of the organization of those receptors that the drugs interact with.

Most quantitative and qualitative characteristics of drug effect also depend on such physico-chemical and physical properties as solubility in water and lipids. The characteristics of powdered compounds depend on the size of the particles, the volatile substances — on volatility range, etc. Ionization rate is of great importance. For instance, muscle relaxants, structurally related to secondary and tertiary amines, are less ionized and less active than completely ionized quaternary ammonium compounds.

B) Doses and concentrations

Drug action is defined by their dose to a great extent. Changes in their dose (concentration) influence speed of onset of effect, its intensity, duration and sometimes modality. Usually an increase in dose (concentration) minimizes latent period and increases intensity and duration of the effect.

Dose is the amount of a substance per one intake (usually designated as a single dose).

It is necessary to be aware not only of the dose meant for one intake (*pro dosi*), but also of the daily dose (*pro die*).

Dose is measured in grams and gram fractions. For more accurate dosing of drugs their amount is counted per 1 kg of body mass (for example, mg/kg, microgram/kg). In some cases drug dosage is preferably counted by body surface area (per 1 m^2).

Minimal doses, in which drugs cause primary biologic effect, are called threshold, or minimally active. Practical medicine usually uses average therapeutic doses, i.e. doses in which drugs cause necessary pharmacotherapeutic action in the majority of patients. If after administration of these doses the effect is not marked enough, the dose is increased up to the maximum therapeutic one. Toxic doses are doses in which drugs cause harmful toxic effects on the organism (Fig. II.16).

The interval between minimal therapeutic dose (concentration) and minimal toxic dose (concentration)is called *therapeutic window*. For safety use of drugs this interval has to be wide enough.

In experiments on animals for similar drugs characteristic the term *therapeutic index* (TI) is used. TI = LD_{50} :ED_{50}. LD_{50} (median lethal dose) – is the dose that produces death in 50% of animals. ED_{50} (median effective dose) – is the dose that desired therapeutic effect in 50% of animals.

In some cases drug dose is calculated for the full treatment course (course dose). It is especially important for the administration of antimicrobial drugs (antibiotics).

If there is a necessity to quickly achieve high concentration of drug in the body, the first dose (loading dose) exceeds the following ones.

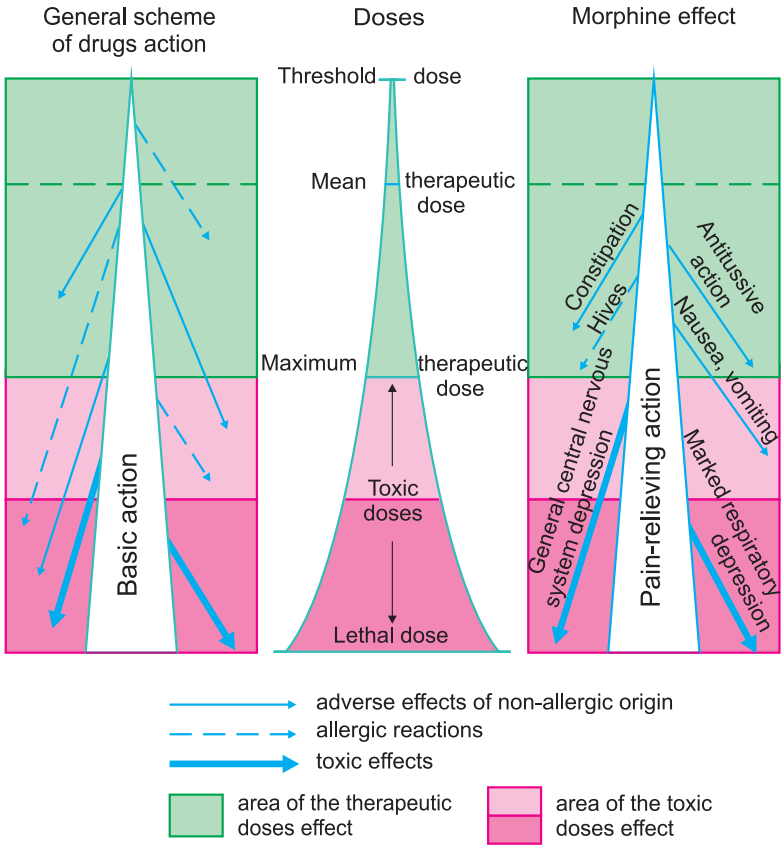

Fig. II.16. Doses, pharmacotherapeutic and adverse effects of drugs (basic, side and toxic effects of morphine are used as an example).

For inhaled drugs (for example, gaseous and volatile substances for general anesthesia) their concentration in the inhaled air is of high importance (indicated in volume percent).

C) Repeated administration of drugs

In repeat drug administration their effect may both increase and decrease.

The increase in effect of a number of drugs is associated with their ability to accumulate (cumulation[1]). *Cumulation* means storage of pharmacological substance in the body. It is typical for long-acting drugs that are released slowly or are steadily bound in the body (for example, some cardiac glycosides from the *Digitalis* group). Cumulation of drug after repeated administration may be the cause of toxic effects. Therefore such drugs have to be dosed considering cumulation, by gradually decreasing the dose or increasing intervals between drug intakes.

Decrease of drug effect after repeated administration (tolerance[2]) is observed with various drugs (opioid analgesics, antihypertensives, laxatives, etc.). It may be associated with the decrease in drug absorption, increase in its inactivation rate and (or) increase in

[1] From Latin *cumulus* — a heap.
[2] From Latin *tolerare* — to endure.

elimination. Tolerance to a number of drugs may be associated with a decrease in sensitivity of receptors (desensetization) to them or with a decrease in the number of these receptors in tissues (downregulation).

When tolerance develops, for the initial effect the drug dose needs to be increased or the drug has to be substituted with another one. If substitution is considered, it has to be remembered that *cross-tolerance* to the drugs, interacting with the same receptors (substrates), may occur.

A special type of tolerance is *tachyphylaxis*[1] — tolerance that occurs very quickly, sometimes after the first administration of a drug. For example, ephedrine, being repeatedly administered with the interval of 10–20 min, causes a smaller increase in arterial blood pressure after subsequent doses compared with the first injection.

Repeated administration of some drugs (usually neurotropic) leads to the development of drug dependence (Table II.5). It appears as a compulsion to take a drug, usually for the purpose of improving mood, well-being and deceasing unpleasant experiences and symptoms, including symptoms of withdrawal of the offending drug. Psycho-

Table II.5. Examples of drugs causing drug dependence.

Drugs	Drug dependence		Tolerance
	psychological	physical	
Morphine, heroin, codeine and other opioids	+	+	+
Barbiturates	+	+	+
Benzodiazepines	+	+	+
Ethyl alcohol	+	+	+
Cocaine	+	–	–
Indian hemp (marijuana, hashish)	+	–	±
LSD-25 (lysergic acid diethylamide)	+	–	+

logical and physical drug dependence can be distinguished. In case of *psychological drug dependence* discontinuation of drug administration (for example, cocaine, hallucinogens) causes only emotional discomfort. *Physical drug dependence* develops after the administration of some drugs (morphine, heroin). It is a more severe stage of dependence. Discontinuation of the drug in this case causes severe health conditions which, besides dramatic psychological changes, include various and often serious somatic disorders, associated with dysfunction of most body systems. It may even lead to death. This is called *abstinence syndrome*[2], or *withdrawal effect*.

Prevention and treatment of drug dependence are a serious medical and social issue.

D) Drug interactions

In medical practice patients often take several drugs simultaneously. These drugs may interact with each other, changing intensity and character of the basic effect and its duration as well as intensifying or weakening adverse and toxic effects.

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[1] From Greek *tachys* — quick, *phylakterion* — protection.

[2] From Latin *ab* — of, away; *tenere* – to hold; Greek: *syn* – with, *drome* – run.

Drug interaction may be classified in the following way.

- Pharmacological interaction:
  - ∨ based on the change in drugs pharmacokinetics;
  - ∨ based on the change in drugs pharmacodynamics;
  - ∨ based on the change of physico-chemical interaction of drugs in the body media.
- Pharmaceutical interaction

  Combinations of different drugs are often used for intensifying or combining effects useful for medical practice. For example, adding certain psychotropic drugs to opioid analgesics substantially increases pain-relieving effect of the latter. Drugs that contain antibacterial and antifungal agents with steroid anti-inflammatory substances can be another useful combination. There are quite a few such examples. At the same time combining drugs can lead to adverse effects, and this is called *drug incompatibility*. This incompatibility is manifested either by weakening, full loss or change of character of the pharmacotherapeutic effect, or by intensifying side or toxic effects (so-called *pharmacological incompatibility*). It can happen with combined administration of two or more drugs. For instance, drug incompatibility may be the cause of hemorrhages, hypoglycaemic coma, seizures, hypertensive crises, pancytopenia, etc. Incompatibility may also occur in preparation and storage of drugs combination (*pharmaceutical incompatibility*).

A. Pharmacological interaction

Pharmacological interaction occurs when one drug changes the pharmacokinetics and (or) pharmacodynamics of the other drug. *Pharmacokinetic type of interaction* can be associated with the failure of absorption, metabolism, transport, storage and elimination of one of the drugs. *Pharmacodynamic type of interaction* is the result of direct or indirect drug interaction on the level of receptors, ion channels, cells, enzymes, organs or physiologic systems. In this case the main effect may change in quantity (be intensified or weakened) or in quality. Also, *chemical and physico-chemical drug interaction* can occur after combined administration of two or more drugs.

Pharmacokinetic type of interaction (Table II.6) can appear even at the stage of drug *absorption*, this can change due to different reasons. Examples are: binding of drugs by adsorbing agents (activated charcoal, kaolin) or by anion-exchange resin (for example, hypolipidemic cholestyramine) in the digestive tract, formation of inactive chelating compounds (for example, interaction between tetracycline antibiotics and iron, calcium or magnesium ions). All these types of interaction prevent drug absorption and decrease their pharmacotherapeutic effects accordingly. pH medium is of substantial significance for absorption of a number of drugs. By changing pH of digestive juices it is possible to significantly affect the rate and range of week organic acids and bases absorption. It has been noted that decreasing ionization levels leads to an increase in lipophility of such substances, and this promotes their absorption.

The change in digestive tract peristalsis also affects drug absorption. Increases in peristaltic action caused by cholinomimetics decreases absorption of cardiac glycoside digoxin, while atropine (blocker of muscarining cholinoceptors), decreasing peristalsis, favors digoxin absorption. There are also examples of drug interaction on the level of their penetration through the intestinal mucous membrane (for example, barbiturates decrease absorption of antifungal drug griseofulvin).

Table II.6. Examples of pharmacokinetic drug interaction.

Group of drugs combined		Interaction result of drugs from group I and II	
I	II	effect	mechanism
Anticoagulants of indirect action (warfarin, etc.)	Almagel	Weakening of anticoagulant action of drugs from Group I	Almagel hinders absorption of the drugs from Group I in the gastro-intestinal tract
Anticoagulants of indirect action (warfarin, etc.)	Cholestyramine	Weakening of anticoagulant action of drugs from Group I	Cholestyramine binds drugs from Group I in the intestinal lumen and decreases their absorption
Salicylates (acetylsalicylic acid, etc.)	Phenobarbital	Weakening of salicylates effect	Phenobarbital intensifies hepatic metabolism of salicylates
Opioid analgesics (morphine, etc.)	Nonselective MAO inhibitors	Increase and prolongation of drug effect from Group I with possible respiratory depression	Nonselective MAO inhibitors depress hepatic inactivation of drugs from Group I
Synthetic antidiabetic drugs (chlorpropamide, etc.)	Phenylbutazone	Intensifying hypoglycaemic effect up to the coma	Phenylbutazone displaces drugs from Group I from binding with blood plasma proteins, increasing their blood concentration
Salicylates (acetylsalicylic acid, etc.)	Antacids, having systemic effect	Some weakening of salicylates action	Antacids decrease reabsorption of salicylates in kidneys (in alkaline medium), increasing their elimination with urine. At the same time blood concentration of salicylates decreases

Inhibition of enzyme activity may also affect absorption. Thus, antiepileptic drug phenytoin inhibits folate deconjugase and impairs absorption of folic acid from food. It results in the development of folic acid deficiency.

Some drugs (almagel, liquid petrolatum) form a layer on the surface of the digestive tract mucous membrane that may hinder drug absorption.

Drug interaction can also occur at the stage of their *binding with serum proteins* (mainly with albumins). One drug may displace another from the complex with plasma proteins. Thus, anti-inflammatory drugs indomethacin and phenylbutazone release indirect anticoagulants (coumarin groups) from the complex with plasma proteins. Concentration of the free fraction of anticoagulants increases, which may lead to hemorrhages. In a similar way phenylbutazone and salicylates increase plasma concentrations of the free fraction of hypoglycaemic drugs (chlorpropamide-like) and may cause hypoglycaemic coma.

Some drugs are able to interact on the level of drug *biotransformation*. There are drugs which increase (induce) activity of the microsomal enzymes of the liver (phenobarbital, phenytoin, griseofulvin, etc.). The metabolism of most drugs increases in the presence of these drugs, and this decreases intensity and duration of their effect (as well as activity of enzymes inducers themselves). However, in clinical settings this interaction manifests distinctly enough only with the use of large doses of enzyme inducers for quite a long period of time.

Drug interaction can result from the inhibition of microsomal and nonmicrosomal enzymes. For example, xanthine oxidase inhibitor (gout treatment medication allopurinol) increases toxicity of antitumor drug mercaptopurin (intensifies its depressing action on hematopoiesis).

Desulfiram, used in alcohol dependence treatment, inhibits aldehyde dehydrogenase and increases toxic effects of alcohol by impeding its metabolism.

Elimination of drugs can also be substantially changed with combined drug administration. It has been already noted that reabsorption of week organic acids and bases in renal tubules depends on pH values of the primary urine. It is possible to increase or decrease the degree of ionization of the drug by changing its pH. The lower the ionization, the higher the lipophility of the drug and the more intensive its reabsorption in the renal tubules. More ionized drugs are poorly reabsorbed and are eliminated with urine to a greater extent. Sodium hydrocarbonate is used to alkalize urine, ammonium chloride is used to acidify it (there are other drugs with similar action). In combined drugs administration their secretion in the renal tubules may be impaired. For example, probenecid inhibits secretion of penicillins in the renal tubules and thereby prolongs their antibacterial effect.

It has to be considered, that drug interaction can change their pharmacokinetics by several mechanisms [for example, barbiturates affect absorption and metabolism of ethylbiscoumacetate (neodicoumarinum)].

Pharmacodynamic type of interaction is based on specificities of their pharmacodynamics (Table II.7). Interaction at the level of receptors mainly occurs with ago-

Table II.7. Examples of pharmacodynamic drug interaction.

Group of drugs combined		Interaction result of drugs from group I and II	
I	II	effect	mechanism
1	2	3	4
Neuromuscular blockers of depolarizing action (suxamethonium)	Cholinesterase inhibitors	Substantial intensification and prolongation of depolarizing action of neuromuscular blockers	Cholinesterase inhibitors prevent hydrolysis of acetylcholine, which is the synergist of suxamethonium (both compounds cause depolarization of the subsynaptic membrane)
α-Adrenoblockers (phentolamine, etc.)	Epinephrine	Decrease in vasopressor action of epinephrine or its «inversion» (hypotensive effect appears)	α-Adrenoblockers are antagonists of epinephrine on α-adrenoceptors. When α-adrenoceptors are blocked, stimulating effect of epinephrine on β-adrenoceptors of the blood vessels shows up
Sympatholytics (reserpine, etc.)	Sympathomimetics (ephedrine, etc.)	Weakening of sympathomimetic action	Sympatholytics are antagonists of sympathomimetics in their effect on the release of norepinephrine from adrenergic endings.
Halothane	Epinephrine	Cardiac arrhythmias	Halothane increases sensitivity of myocardium to epinephrine action

Cont. table II.7

1	2	3	4
Acetylsalicylic acid	Anticoagulants (warfarin, etc.)	Hemorrhages	Acetylsalicylic acid causes ulceration of the gastric mucosa, decreases blood concentration of prothrombin and decreases aggregation of platelets. On this background anticoagulants promote hemorrhage
Antipsychotic drugs (chlorpromazine, haloperidol), anxiolytics (diazepam, etc.)	Ethyl alcohol	Substantial increase of CNS inhibition by ethyl alcohol	Antipsychotics and anxiolytics potentiate the inhibitory effect of ethyl alcohol on CNS
Penicillin	Tetracyclines, Chloramphenicol	Weakening of antimicrobial action of penicillin	Penicillin affects only dividing cells. At the same time tetracycline and chloramphenicol inhibit division of microorganisms
Antibiotics from the aminoglycoside group (streptomycin, neomycin, kanamycinum)	Neuromuscular blockers (curare-like)	Intensification of myoparalytic action of neuromuscular blockers	Aminoglycosides and neuromuscular blockers are synergistic in the inhibition of the neuromuscular transmission
Antibiotics from aminoglycosides group	Antibiotics from the aminoglycoside group	Increase in ototoxicity and curare-like action	Synergism (summing up of effects) of antibiotics from one group
Sulfonamide drugs	Procaine	Weakening of antimicrobial action of sulfonamide drugs	Procaine hydrolysis produces *p*-amino-benzoic acid that is a competitive antagonist of sulfonamide drugs

nists and antagonists. One compound can intensify or weaken the effect of the other one. In case of *synergism*[1] drug interaction leads to an increase in effect.

Drug synergism may present either as a simple summing up or potentiation of effect. Summed (additive[2]) effect represents the actual sum of effects of the individual drugs (for example, this is how additive effects of anesthetics occur). If during the administration of two drugs the total effect exceeds (sometimes significantly) the sum of both drug effects, it indicates potentiation (for example, antipsychotic drugs potentiate the effects of general anesthetics).

Synergism may be direct (if both compounds affect one substrate) or indirect (if their effects have different localization).

The ability of a drug to decrease the effect of the other one is called *antagonism*. By analogy with synergism, direct and indirect antagonism are distinguished (interaction on the level of receptors is described above).

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[1] From Greek *syn* — together, *ergos* – work.

[2] From Latin *addition-ad* — to; *addere* – to put.

Synergoantagonism occurs when some effects of the combined drugs are intensified, and others are weakened. For example, α-adrenoblockers lead to a decrease in epinephrine stimulation of vessel α-adrenoceptors, but its effect on vessels β-adrenoceptors becomes more marked.

The chemical and physicochemical interaction of drugs in body media is mostly used to treat an overdose or acute poisoning with drugs. The ability of adsorbing drugs to hinder drug absorption from the digestive tract has already been mentioned. An overdose of heparin anticoagulant is treated with its antidote protamine sulphate that inactivates heparin due to the electrostatic interaction with it. This is an example of physico-chemical interaction.

Chelator formation can illustrate chemical interaction. Calcium ions are bound by EDTA[1] (disodium salt) (trilon B; Na_2EDTA). Lead, mercury, cadmium, cobalt and uranium ions are bound by tetacin-calcium ($CaNa_2EDTA$); copper, mercury, lead, iron and calcium ions — by penicillamine.

Therefore, there are various types of pharmacological drug interactions (see Tables II.6 and II.7).

B. Pharmaceutical interaction

There are cases of pharmaceutical incompatibility when during the production process, storage or mixing of the drugs in one syringe interaction of the components of the mixture occurs. The resultant changes can cause the drugs to become unsuitable for common use. At the same time pharmacotherapeutic activity of the initial components decreases or disappears. In some cases new and sometimes adverse (toxic) properties appear.

Pharmaceutical incompatibility can be associated with chemical, physical and physico-chemical properties of substances. For example, incompatibility may be caused by insufficient or total insolubility of substances in a solvent, coagulation of drug formulation, emulsion layering, dampening and melting of powders due to their hygroscopic property. When drugs are co-prescribed by mistake, there may be a change in color, taste, smell or consistency of the drug formulation as a result of chemical interaction.

7. IMPORTANCE OF INDIVIDUAL CHARACTERISTICS OF THE HUMAN BODY AND ITS STATE FOR THE MANIFESTATION OF THE DRUG EFFECT

A) Age

Sensitivity to drugs changes with age. That is why so-called perinatal pharmacology that studies specificities of drug effect on the fetus (from 24 weeks of pregnancy up until delivery) and on the newborn (up to 4 weeks of life) is distinguished. With regard to drug sensitivity, a fetus in the last trimester and newborns in the first month of life are significantly different from adults. This is mainly due to the insufficiency of most enzymes, renal func-

[1] Ethylene diamine tetracetic acid.

tion, increased permeability of the blood-brain barrier and the underdevelopment of the CNS. During this period of life, receptors have different sensitivity to drugs. For example, newborns are more susceptible to some drugs, affecting the CNS (in particular to morphine). Chloramphenicol is very toxic for them and may even cause death. This occurs due to the fact that the liver lacks the necessary enzymes for its detoxification. At an early age children can not be prescribed drugs that intensify secretory activity of the glands (bronchial, nasal mucosa, other), because it can disturb respiration and be a cause of respiratory disease.

The field of pharmacology, studying specificities of drug effects on child's organism, is called pediatric pharmacology.

In elderly and old patients drug absorption is delayed, their metabolism is less effective, drugs elimination via kidneys is reduced. In general, sensitivity to most drugs in elderly and old patients is increased, and therefore the doses should be reduced. Besides minimally toxic drugs should be selected for use in this population.

It is important to know specificities of drug effect in elderly and old patients (so-called geriatric[1] pharmacology) because the proportion of these age groups among the general population has significantly increased.

B) Gender

Animal experiments have shown that males are less susceptible to a number of substances (nicotine, strychnine), than females. Some differences in the metabolism of some drugs are also associated with gender. There are also some clinical observations. For example, paracetamol clearance occurs faster in males than in females. In menopausal females, intestinal absorption of calcium ions is delayed. Bioavailability of verapamil in females is higher than in males. Oxygenation of diazepam occurs faster in females. Antiarrhythmic drugs cause arrhythmogenic effect (so-called «torsade de pointes») in females more often than in males. To relieve postoperative pain males need higher morphine doses than females.

In general, this issue is not studied enough. For each drug it is important to find out the causes of gender differences in pharmacokinetics and pharmacodynamics.

C) Genetic factors

Patients can be genetically predisposed to drug sensitivity. It is manifested both in quantity and in quality of response to a drug. For example, genetic insufficiency of plasma cholinesterase lengthens the duration of the effect of a neuromuscular blocker suxamethonium to last 6–8 h and more (in normal conditions the effect of suxamethonium lasts 5–7 min).

It is known that the acetylation rate of antituberculosis drug isoniazid varies rather widely. There are individuals with rapid and slow metabolizing activity. People with slow isoniazid inactivation have a deficiency of genes regulating acetylating enzyme synthesis.

There are examples of atypical reactions to drugs (*idiosyncrasy*[2]). For example, antimalarial drugs from the 8-aminoquinolone group (primaquine, other) can cause

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[1] From Greek *geron* — old man, *iatros* — physician.

[2] From Greek *idios* — personal, *syn* — together, *krasis* –mixture.

hemolysis in individuals with genetic enzymopathy (deficiency of glucose 6-phosphate dehydrogenase enzyme leads to the formation of quinone that does have hemolytic action). There are other drugs with potential hemolytic effects. They include aminoquinolones (primaquine, chloroquine), sulfones (dapsone), sulfonamides (sulfacyl sodium, sulfamethoxypyridazine), nitrofurans (furazolidone, nitrofurantoin), non-opioid analgesics (acetylsalicylic acid) and other drugs (nalidixic acid, quinine, quinidine, chloramphenicol).

To clarify the role of genetic factors in individual sensitivity to drugs is the main aim of a special pharmacological science — *pharmacogenetics*.

D) General state of the organism

Drug effect can depend on general state, particularly on pathology in which they are administered. Thus, antipyretics decrease body temperature only in the presence of fever (they do not act if the body temperature is normal). Cardiac glycosides affect blood circulation only in the presence of heart failure. The higher the hypotensive action of ganglionic blockers, the higher the tone of sympathetic innervation. In hyperthyroidism, sensitivity of myocardium to epinephrine is increased.

Diseases, associated with renal and hepatic failure, change elimination and the metabolism of drugs accordingly. At the same time other parameters can also be changed, such as binding with plasma proteins, bioavailability and distribution.

Drug pharmacokinetics changes in pregnancy and obesity.

E) Significance of circadian rhythms

Circadian rhythm[1] are of great importance for physiologic functions. It is widely known, that the interchange of wakefulness and sleep substantially affect the activity of the nervous system and endocrine glands and the state of other organs and systems. It also affects the sensitivity of the organism to different drugs. Investigation of the dependence of pharmacological effect on circadian rhythms is one of the main objectives of a new trend called chronopharmacology. The latter includes both *chronopharmacodynamics* and *chronopharmacokinetics*.

Depending on the time of day, drugs effect may be changed not only in quantity, but sometimes in quality. In most cases their most marked effect is witnessed during the period of maximal activity (in people — in day-time, in nocturnal animals — in the dark). For example, in humans analgesic morphine is more active in the second half of the afternoon than early in the morning or at night-time. There are daily fluctuations in the production of endogenous peptides with analgesic activity (encephalins and endorphins). In angina rectoris, nitroglycerin is more effective in the morning, than in the second half of the afternoon.

Drug toxicity changes significantly with the circadian rhythm. Thus, animal experiments done at different times of day have shown lethal outcome to be fluctuating from 0 to 100%.

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[1] From Latin *circa* — about, *dies* — day. These are cyclic fluctuations of biologic processes in the interval of 20–28 h.

Pharmacokinetic parameters also depend on daily rhythms. In particular, the greatest absorption of the antifungal drug griseofulvin in humans occurs approximately at noon. The intensity of metabolism can change throughout the day (for example, metabolism of hexobarbital). Kidney function and their ability to excrete drug changes significantly, depending on the time of day. For amphetamine it is known that human kidneys excrete especially large amounts of the drug early in the morning (which is probably connected with urine pH fluctuations). After oral administration lithium is excreted in smaller amounts at night-time rather than in day-time.

Therefore, pharmacodynamics and pharmacokinetics of drugs depend on circadian rhythms. It has to be added that drugs themselves can affect phases and amplitude of daily rhythm. It also has to be considered, that the result of their interaction with the body at different times of the day can change with pathologic conditions and diseases.

Even though the volume of information in chronopharmacology is limited, its significance for the rational dosage of drugs by using the correct time of their administration is doubtless. It is known that physiologic functions depend also on seasonal rhythms, which can influence drug effects.

8. MAIN TYPES OF DRUG TREATMENT

Prophylactic use[1] of drugs means prevention of certain diseases. Disinfectants, chemotherapeutic drugs and other are used for this purpose.

Etiotropic[2] (causal[3]) therapy is aimed to eliminate the cause of the disease (thus, antibiotics affect bacteria, antimalarial drugs — malaria plasmodia).

The main task of symptomatic therapy is the elimination of unwanted symptoms (for example, pain), and thus significant influence on the basic pathologic process. Therefore, in many cases symptomatic therapy plays the role of the treatment of pathogenesis of the disease[4].

Replacement therapy is used to treat the deficiency of natural biogenic substances. In the failure of endocrine glands (in diabetes mellitus, myxedema) appropriate hormones are administered. Duration of such therapy is measured in months and years.

9. PRINCIPAL AND ADVERSE EFFECT. ALLERGIC REACTIONS. IDIOSYNCRASY. TOXIC EFFECTS

Drugs are administered to obtain a certain pharmacotherapeutic effect: for example, to relieve pain. Hypotensive drugs are used to decrease arterial blood pressure, etc. This is a manifestation of a drug's principal effect due to which they are used in practical medicine. However, along with desirable effects all drugs have adverse effects, including non-allergic side effects, allergic reactions, toxic and other effects.

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[1] From Greek *pro* — before, *phylaxis* — a guard.
[2] From Greek *aitia* — cause, *tropos* — direction.
[3] From Latin *causa* — cause.
[4] From Greek *patheia* — suffering, *genesis* — origin.

Non-allergic side effects include only those effects that occur in the administration of therapeutic doses and that are in the range of their pharmacological action (see Fig. II.16). Thus, phenobarbital, administered as an antiepileptic drug, may cause drowsiness. Pain-relieving morphine in therapeutic doses causes euphoria and stimulates the tone of gastrointestinal sphincters.

Side effects can be primary and secondary. Primary side effects occur as a direct effect of the drug on a certain substrate (for example, nausea and vomiting occurring due to the irritant action of the drug on the gastric mucosa). Secondary side effects refer to adverse reactions developing indirectly (for example, hypovitaminosis due to suppression of the intestinal flora with antibiotics).

Adverse effects of drugs vary in character, intensity and duration. Side effects may target the nervous system, blood and hematopoiesis, organs of blood circulation, respiration, digestion, as well as kidneys, endocrine glands, etc. Some side effects are tolerated relatively easily (moderate nausea, headache, so on); others can be severe and even life threatening (liver damage, leucopenia, aplastic anemia).

Adverse effects, caused by drugs, also include allergic[1] reactions. They occur rather often and regardless of the drug dose administered. In allergic reactions drugs act like antigens (allergens). *Drug allergies (hypersensitivity)* are usually subdivided into 4 types.

Type I (immediate allergy). This type of hypersensitivity is associated with involvement of IgE-antibodies in the reaction. It is manifested by hives, angioedema, rhinitis, bronchospasm and anaphylactic shock. Such reactions occur after administration of penicillins, sulfonamides, etc.

Type II. In this type of allergy IgG- and IgM-antibodies, activating complement system, interact with circulating blood cells and cause their lysis. Thus, methyldopa can cause hemolytic anemia, quinidine — thrombocytopenic purpura, a number of drugs (for example, metamizole) sometimes cause agranulocytosis.

Type III. This type of drug allergy probably involves IgG- as well as IgM- and IgE-antibodies (+ complement). "Antigen — antibody — complement" complex interacts with vascular endothelium and damages it. So-called serum sickness occurs. It is manifested with hives, arthralgia, arthritis, lymphadenopathy and fever. Penicillin, sulfonamides, iodines and other drugs may cause serum sickness.

Type IV. In this case reaction is mediated through cellular mechanisms of immunity, including sensitized T-lymphocytes and macrophages. It occurs after local application of the drug and manifests as contact dermatitis.

Idiosyncrasy (see above) means specific adverse effect to an individual. Drug-induced idiosyncratic reaction can be very serious (hepatitis, agranulocytosis, lupus etc.).

In doses exceeding therapeutic, drugs can cause toxic effects. The latter usually causes one or other disorder of organ and system functions (hearing loss, vestibular disorders, blindness caused by optic nerve lesion, marked disorder of myocardial conduction, liver damage, hematopoiesis problems, suppression of vital centers of medulla oblongata).

The main cause of toxic effects is overdose — accidental or deliberate intake of doses that exceed the maximum tolerance doses. Alternatively, there may be accumulation of toxic concentrations of drugs in the body as a result of metabolism failure (for example, in liver pathology) or their delayed elimination (in some renal diseases).

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[1] From Greek *allos* — different, *ergon* — activity.

Drugs administered during pregnancy can affect the embryo and fetus. These effects include teratogenic[1] action of drugs that leads to the birth of children with various abnormalities.

Attention to the possible teratogenic action of drugs was attracted by the tragedy, caused by thalidomide administration in a number of countries. This drug was introduced into medical practice as a sedative and hypnotic agent. However, thalidomide proved to have marked teratogenic properties. During the number of years when it was used several thousand children were born with various abnormalities (phocomelia[2], amelia[3], facial hemangioma, gastrointestinal abnormalities, etc.). Due to these accidents, there is currently much more awareness and caution about using any old or new drugs during pregnancy.

An attempt has been made to create adequate animal models to study the teratogenic action of drugs, though these studies were not successful. To present day there are no sufficiently convincing experimental methods to establish the potential teratogenicity of drugs. The problem is that an abnormality in animals can be caused by a lot of substances, including drugs widely used in medicine that, according to the data available, do not have teratogenic effects on the human embryo. Thus, only negative results are of importance. If a drug does not cause developmental abnormalities in animals, there are reasons to consider that they will not occur in humans. But if the compound is teratogenic in animals, it does not mean that this effect will occur in human. Nevertheless, such drugs have to be used with caution due to potential teratogenicity. Since there is an uncertainty in determining the risk of teratogenicity, females in the first 2–3 months of pregnancy, when the embryo's main organs are forming, are advised to avoid drug intake without absolute need . The first trimester of pregnancy is considered the most dangerous regarding teratogenic action (especially the first 3–8 weeks, i.e. organogenesis period). In this period the risk of severe abnormality of the embryo is high.

At the same time it has to be considered that drugs may negatively affect the embryo and fetus in a way that is not associated with disorder of organogenesis through teratogenic action. It can occur as a result of adverse or toxic effects of drugs. It can manifest itself in different stages of pregnancy. If such effects occur before the 12th week of pregnancy, they are called embryotoxic, later — fetotoxic[4].

In the administration of drugs to pregnant women it has to be considered, that when the drugs pass the placenta they can affect the fetus. Thus, streptomycin, administered to a pregnant woman, can cause deafness in her fetus (VIII pair of cranial nerves can be damaged). Tetracyclines affect fetal bone formation. If a mother is suffering from morphine dependence, the newborn may also have physical dependence on morphine. If before delivery the woman is administered anticoagulants, the newborn may have hemorrhages. There are many more such examples. This is the evidence that various chemical compounds (lipophilic) pass through placenta. Therefore,

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[1] From Greek *terasatos* — monster, *genesis* – be produced.

[2] Phocomelia — flipperlike limbs. From Greek *phoke* — seal, *melos* — limb.

[3] Amelia — absence of limbs.

[4] From Latin *fetus* — offsping;Greek: *toxicon* – poison.

pregnant women should undergo pharmacotherapy only if there are strict indications. It is necessary to choose very carefully the least toxic and previously well-tested drugs.

There is also a possibility that drugs will get into newborns through the mother's breast milk and affect them. For example, penicillin can cause allergic reactions, sulfonamides — hemolytic anemia, anticoagulants — hemorrhage.

In producing new drugs one has to bear in mind the potential possibility of such serious adverse effects as chemical mutagenicity and carcinogenicity. Mutagenicity[1] is the ability of a drug to cause steady damage to an embryo's germ cells and its genetic material, which causes genotype alteration of the offspring. Carcinogenicity[2] is the ability of a drug to cause development of malignant tumors.

Such adverse effects can also occur due to incorrect drug combination — drug incompatibility (see above).

10. GENERAL PRINCIPLES OF THE TREATMENT OF ACUTE DRUG POISONING[3]

Acute chemical poisoning, including that with drugs, occurs rather often. Poisonings can be accidental, intentional (suicidal[4]) and associated with occupational hazards. Most common are poisonings with ethyl alcohol, hypnotic drugs, psychotropic drugs, opioid and non-opioid analgesics, organophosphorous insecticides and other compounds.

Special toxicological centers and departments are established to treat chemical poisonings. The main task of the treatment of acute poisoning is to eliminate the drug causing intoxication from the body. In severe patients' conditions this should be preceded by general therapeutic and resuscitation measures aimed at the maintenance of vital systems' function, respiration and blood circulation.

Detoxification principles are as follows. First of all it is necessary to block the drug's absorption at the routes of introduction. If the drug is already partially or fully absorbed, its elimination from the body should be accelerated and its antidotes should be used to neutralize it and eliminate toxic effects.

A) Delay of the absorption of the toxic substances into the blood

Most often acute poisonings are caused by drug intake. That is why one of the most important methods of detoxification is catharsis. Vomiting is induced and gastric lavage is performed. Vomiting is caused mechanically (irritation of the posterior wall of pharynx), by concentrated solutions of sodium chloride or sodium sulphate or admini-

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[1] From Latin *mutatio* — alteration, Greek *genos* — origin.

[2] From Latin *cancer* — crab.

[3] This section refers to general toxicology.

[4] From Latin *sui* — oneself, *cadere* — to kill.

stration of emetic drug — apomorphine. In poisoning with drugs causing damage to the mucous membranes (acids and alkali), vomiting should not be induced otherwise additional lesions of the esophageal mucous membrane will occur. Besides, drug aspiration and inhalation damage of respiratory tract can occur. Gastric lavage with a stomach pump is the most effective and safe. First, gastric contents are removed, then the stomach is washed out with warm water, an isotonic solution of sodium chloride or permanganate potassium solution with the addition of activated charcoal and other antidotes, if necessary. The stomach is lavaged several times (every 3–4 h) until it is completely drug-free.

To block drug absorption from the intestines, adsorbing drugs (activated charcoal) and laxatives (saline laxatives, petrolatum) are given. Intestine lavage is also performed.

If the drug that caused intoxication has been applied onto the skin or mucous membranes, it is necessary to thoroughly wash them (best with running water).

If the toxic agent was inhaled, its inhalation must be stopped (move the victim from the poisoned atmosphere or put a gas-mask on him).

In subcutaneous introduction of a toxic agent, its absorption from the site of application can be delayed with injections of epinephrine solution around the site of its introduction, as well as with cooling of this region (ice pack is placed on the skin). If possible, a tourniquet should be applied which would hinder blood flow and cause venous congestion at the site of drug introduction. All these activities minimize systemic toxic effect of the drug.

B) Elimination of the toxic substance from the body

If the drug has been absorbed and has systemic action, the main efforts must be aimed at its most rapid elimination from the body. Forced diuresis, peritoneal dialysis, hemodialysis, hemosorption, blood substitution and other methods are used for this purpose.

Methods of *forced diuresis* are the combination of loading the patient with water and administration of active diuretics (furosemide, mannitol). In some cases alkalinization and acidification of urine (depending on the properties of the drug) promotes more rapid elimination of the drug (due to decrease of its reabsorption in the renal tubules). Forced diuresis enables elimination only of free substances not bound with proteins and lipids in the blood. When this method is used, electrolyte balance must be carefully maintained, since it can be disturbed due to the elimination of a significant amount of ions from the body. In acute cardio-vascular failure, marked renal failure and a risk of brain or pulmonary edema, forced diuresis is contraindicated.

Hemodialysis and peritoneal dialysis[1] are other methods used for this purpose. In *hemodialysis* (artificial kidney) blood passes through dialyser with semipermeable membrane and becomes essentially free from protein-bound toxic substances (for example, barbiturates). Hemodialysis is contraindicated in abrupt decrease of arterial blood pressure.

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[1] Dialysis (from Greek *dial* — through, *lysis* – set free) — separation of colloid particles from the solute.

Peritoneal dialysis is peritoneal lavage with electrolyte solution. Depending on the type of poisoning, certain dialysis fluids that aid the most rapid elimination of the drugs into the peritoneal cavity, are used. Along with dialysis solution, antibiotics are administered to prevent infection. In spite of the high efficiency of these methods, they are not universal since not all chemical compounds are dialysed well (i.e. do not pass through the semipermeable membrane of the dialysis machine during hemodialysis or through peritoneum in peritoneal dialysis).

Another detoxification method is *hemosorption*. In this method toxic substances present in the blood are adsorbed on special sorbents (for example, on granular activated charcoal with blood protein covering). This method enables successful body detoxification to be performed in poisonings with antipsychotic drugs, anxiolytics and organophosphorus compounds, etc. It is important to note, that this method is also effective in those cases when the drugs are poorly dialysed (including drugs bound with blood proteins), and hemodialysis does not give a positive result.

In the management of acute poisonings blood substitution is also used. In such cases bloodletting is combined with the transfusion of donor blood. This method is mostly indicated in poisoning with drugs directly affecting the blood, for example, causing methemoglobin formation (nitrites, nitrobenzenes and others). Also, this method is very effective in treating poisoning with high-molecular weight compounds that are firmly bound to plasma proteins. This procedure is contraindicated in severe disorders of blood circulation and thrombophlebitis.

In recent years *plasmapheresis*[1] has gained wider use in the management of poisoning with certain drugs. In plasmapheresis, only plasma is removed without other blood contents' loss. After this, plasma is replaced with donor plasma or electrolyte solution with albumin.

Sometimes detoxification is performed through the chest lymphatic duct removing the lymph (*lymphorrhea*). *Lymphodialysis* and *lymphosorption* are possible. These methods are not very useful in the treatment of acute drug poisoning.

If the poisoning occurred with a substance that is eliminated via the lungs, then forced breathing is one of the most important ways of treating this kind of intoxication (for example, with inhaled anesthesia drugs). Hyperventilation may be induced by a respiration stimulant — carbogene, as well as by artificial ventilation.

Intensification of the biotransformation of toxic substances in the body does not play a substantial role in the management of acute poisoning.

C) Counteracting the effect of an absorbed toxic compound

If the offending drug has been established, body detoxification with the help of antidotes[2] has to be performed.

Antidotes are drugs used for specific treatment of chemical poisonings. They include drugs that inactivate poisons either via chemical or physical interaction, or due to

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[1] From Greek *plasma* — plasma, *aphairesis* — taking away.

[2] From Greek *antidoton* — antipoison.

pharmacological antagonism (on the level of physiologic systems, receptors etc.)[1]. Thus, in poisoning with heavy metals the treatment includes compounds that form non-toxic complexes with them (for example, unithiol, D-penicillamine, CaNaEDTA). There are antidotes that enter into the reaction with drugs and release the substrate (for example, oximes — cholinesterase reactivators). Antidotes, used to treat poisoning with methemoglobin-forming drugs acts the same way. In acute poisoning, pharmacological antagonists are widely used (atropine is used to treat poisoning with cholinesterase inhibitors, naloxone — in morphine poisoning, etc.). Usually pharmacological antagonists interact competitively with the same receptors as the offending drugs. Creating specific antibodies to the drugs that are the most frequent cause of acute poisoning has a great potential.

The earlier antidotes are administered in the course of acute poisoning, the more effective they are. If advanced tissue , organs and body systems' damage has occurred and in the terminal stages of poisoning efficacy of antidote therapy is low.

D) Symptomatic therapy of an acute poisoning

Symptomatic therapy plays an important role in the treatment of acute poisoning. It is especially important in poisonings with drugs that do not have any specific antidotes.

First of all it is necessary to maintain vital functions — blood circulation and respiration. Cardiotonics, drugs controlling arterial blood pressure, drugs improving microcirculation in peripheral tissues and oxygen therapy are often used for this purpose. Sometimes respiration stimulants and other methods are also used. Undesirable symptoms that worsen patient's condition are eliminated with appropriate drugs. Thus, seizures can be stopped with anxiolytic diazepam that has a marked anticonvulsant activity. In brain edema, dehydration therapy is performed (with mannitol and glycerin). Pain is relieved with analgesics (morphine, etc.). Great attention has to be paid to acid-base balance. If it is disturbed, necessary correction has to be made. In the treatment of acidosis sodium bicarbonate solutions and trisamine are used, and in alkalosis — ammonium chloride. Water-electrolyte balance is also very important.

Thus, the management of acute poisoning with drugs includes the complex of detoxifying activities in combination with symptomatic and, if necessary, resuscitation therapy.

E) Acute poisoning prevention

The main aim is to prevent acute poisonings. To achieve this it is necessary to write correct drug prescriptions and to store them correctly in medical establishments and home settings. Thus, drugs are not to be stored in the dressers or in the refrigerator together with food. Places of drug storage should be out of reach of children. It is unrea-

[1] More precisely, antidotes are only those anti-poison compounds that interact with poisons physico-chemically (adsorption, formation of sedimentation or non-active complexes). Anti-poison compounds with action based on physiologic mechanisms (for example, antagonistic interaction on the level of «target»-substrate), is referred to as antagonists according to this nomenclature. Though, in practical use all anti-poison compounds regardless of their mechanism of action are usually called antidotes.

sonable to store unnecessary drugs at home. Expired drugs should not be used. Drugs in use must have appropriate labels with the drug name on it. One certainly must strictly follow the doctor's recommendations and dosage when taking a drug. Self-medication, as a rule, should not be tolerated since it often leads to acute poisoning and other adverse effects. It is important to follow safety standards of storage and working with chemical substances in chemicopharmaceutical factories and in laboratories, dealing with production of drugs. Following these requirements can substantially reduce the rate of acute drug poisonings.