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PHARMACOLOGY

Textbook
Second edition

In two parts

Part 1

Ministry of Education and Science of Ukraine
Ministry of Health Care of Ukraine
Sumy State University

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Material of the textbook is given according to the Training Programme in Pharmacology and Medical Prescription. Questions of general and special pharmacology are described at the up to date level. The textbook contains mechanisms of action, pharmacokinetics, pharmacodynamics, indications and contraindications for clinical use, and side effects of main groups of pharmacological drugs. The main attention is paid to data having fundamental meaning for training future doctors. The second edition is substantially revised and supplemented with schemes and information about new drugs.

For students of higher medical educational institutions of the IV level of accreditation.

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INTRODUCTION

Presently, a large number of drugs are used to treat and prevent different diseases. Doctor of any speciality should be able to know them well for correct prescribing pharmacotherapy to patients. In this regard, there is a need for quality training of students of higher medical educational institutions in pharmacology, knowledge of which is basic and integrates theoretical and clinical disciplines. Pharmacology finishes theoretical training of future doctors and is a logical continuation of courses of normal and pathological physiology, biochemistry, microbiology, and anatomy. Therefore, the authors, when presenting the material, considered it necessary to briefly recall physiological, biochemical, immunological, and anatomical knowledge that is necessary for understanding of pharmacodynamics of drugs and their mechanisms of action.

Suggested textbook contains main rules of drug prescription, data of general and special pharmacology. With the aim to form stable skills in students to work with drug nomenclature, the unified nomenclature system of drugs, based on International Nonproprietary Names (*INN*), is given in the textbook. This system is used in modern educational literature of different countries. In most cases, the authors indicate both INN and most commonly used trade names of drugs.

All chapters of the textbook are given in volume that is necessary for clear understanding of principles of action and effective and safe use of drugs. Each pharmacological group is constructed in a unified and logical sequence which facilitates the perception, assimilation and use of information.

Due to large volume of information which should be mastered by students, the authors focus on group properties of drugs and describe the main representatives of groups. At the same time, the same drugs, used for different indications, are described in different chapters (e. g., β-adrenergic antagonists are given in chapters “Antiadrenergic drugs”, “Drugs for treatment of hypertension”, “Drugs for treatment of ischemic heart disease”, and “Antiarrhythmic drugs”).

Main data about drugs are given in one main chapter, and additional information is given in other chapters. Data about pharmacodynamics, pharmacokinetics, clinical applications, and side effects are given for each group of drugs; and, if it is necessary, corresponding data about individual drugs are additionally given.

Suggested textbook contains data about new drugs and modern scientific data. Mechanisms of action and therapeutic indications for drugs are given considering modern data of biochemistry, pathological physiology and fundamental pharmacology. This textbook contains some elements of clinical pharmacology.

A separate chapter of the textbook describes general principles of treatment of acute poisoning by drugs and other toxic substances. Measures to prevent the ingress of poison into the body, inactivation of poisons by antidotes, restriction of poisons action by physiological antagonists, acceleration of poison elimination from the body, and resuscitation measures are given in this chapter. Besides, resuscitation measures at cases of inhibited respiration, collapse, acute heart failure, and bronchoconstriction are considered, especially in acute period of poisoning.

The textbook is recommended for third-year students of higher medical educational institutions. Its structure and content correspond to the curriculum of pharmacology, approved at an interdepartmental meeting of heads of pharmacological departments of higher medical educational institutions.

We will be grateful for any comments and suggestions that may arise from the readers of this textbook.

MEDICAL PRESCRIPTION

Introduction to Medical Prescription

The science about drugs consists of two branches of knowledge: pharmacology and pharmacy.

Pharmacology is the science about interaction between an organism and a drug.

Pharmacy is the science which studies questions of search, processing, preparation, and standardization of medicines. Pharmacy is complex science which includes pharmacognosy, pharmaceutical chemistry, technology of the medicinal form preparation, and prescription.

Prescription is a section of pharmacy, which consists of the prescribing rules and rules of the drug preparations. Accordingly, prescription is divided into pharmaceutical and medical one. Pharmaceutical prescription contains the drug preparation rules. Practically, pharmaceutical prescription is separated in the special sector – medicinal form technology.

Medical prescription includes the rules of drug prescribing. Namely, medical prescription has the important role in the physician's practical activity.

Most important terms of medical prescription are the following.

Medicinal substance (in Latin – "*substantia pharmaceutica*") is one chemical substance or chemical element which is used as the medicinal remedy.

Medicinal remedy (in Latin – "*medicamentum*") is natural or synthetic substance or mixture of some substances which are permitted by the Ministry of Public Health Services for the treatment and prophylactic of the certain diseases.

Pharmacological remedy is substance or mixture of substances with determined pharmacological activity and toxicity which is object for clinical trials. After receiving the sanction for the use in medical practice, the pharmacological remedy is registered in the state register of medications.

Medicinal form is the created state of medicinal remedy (remedies) which is appropriate for the practical use and provides the

ability to reach the necessary therapeutic effect and drug stability during the storage. In dependence to consistency, there are solid, soft, and liquid medicinal forms. In turn, liquid medicinal forms are divided into forms for external use, forms for internal intake, and injections.

The same medicinal remedy may be prescribed in different medicinal forms.

A drug (*preparatum*) is the medicinal remedy in certain medicinal form.

Nowadays, the sources of medications are very diverse. They include mineral substances, nonorganic and organic compounds, vegetable raw materials, animal organs, microbial metabolic products, etc. Prior to the use, medicinal raw materials undergo the appropriate processing. Processing may be simple (drying, grinding) or complex (isolation of active substances). Due to complex processing of vegetable raw material, so-called galenic medications or galenic formulations (tinctures, extracts) are derived.

Galenic medications are drugs which are derived due to maceration of extraction of medicinal raw materials. Besides active substances, galenic medications contain also ballast substances (cellulose, mucus, proteins, tars, etc.). Therefore, galenic medications are not appropriate for parenteral administration. Besides galenic drugs, pharmaceutical industry produces more purified drugs containing maximum of active substances from herbal raw material and minimum of ballast substances. Such medications are called novogalenic drugs. They are appropriate for parenteral administration. For example, opium is medicinal raw material; opium powder is simple preparation; opium tincture is galenic formulation; omnoponum is novogalenic drug; morphine is pure opium alkaloid which is used for parenteral administration in the form of hydrochloride salt solution.

The relationship of different pharmacological terms may be considered by the example of atropine sulfate:

– Belladonna – herbal raw material;

– alkaloid atropine – medicinal substance;

– atropine sulfate – medicinal remedy;

– atropine sulfate in powders, in tablets, in ampules, in eye ointment – drugs.

All drugs are divided into three groups in dependence to a degree of expressiveness of their action upon an organism.

Poisonous drugs (*Venena*, the list A). Drugs with very high toxicity are included into this group. In hospital, these drugs should be stored in a special safe box constantly under lock and key. The safe box should be sealed up after the end of the working day. The strict control should be carried out about an expenditure of these drugs.

Potent medicines (*Heroica*, the list B). Drugs, using of which without medical control can cause different complications, are included into this group. These drugs should be kept in a separate cupboard with an inscription "*Heroica*". After the end of the working day, the cupboard should be closed.

A storage, account, and delivery of poisonous and drastic drugs should be carried out according to the rules approved by the Ministry of Healthcare.

Low-poisonous drugs *(Varia)* are stored in usual cupboards according to the general rules of their storage.

The list of manufactured medicinal remedies and drugs is in the special book called Pharmacopoeia. Pharmacopoeia is the collection of State standards and the obligatory norms determining drug qualities. The following information is in Pharmacopoeia: description of properties, the physical and chemical qualities of medicinal remedies in alphabetic order, and the ways of definition of their suitability to the use. Methods of quantitative definition of medicinal components are also located in Pharmacopoeia.

Based on Pharmacopoeia specifications, it allows carrying out the control over the drug manufacturing and their usage. In Pharmacopoeia, we can find also such important information: the lists of poisonous and drastic drugs, the tables with the maximal single and daily doses for poisonous and drastic drugs (both for adults and children), conditions of the drug storage and delivery, ways of manufacturing of medicinal forms, the methods of biological standardization and so on.

Drugs included in Pharmacopoeia are referred to officinal drugs ("*officina*" – "workshop", "drugstore").

Magistral drugs are medicines prescribed by a physician for a particular case. These medicines are made by a pharmacist in a pharmacy ("*magister*" in Latin means "teacher").

There are two groups of the drug administration routes: enteral routes (through gastro-intestinal tract) and parenteral ones (passing a digestive tube). The enteral routes are oral (by mouth), sublingual (under tongue), transbuccal (behind a cheek), into duodenum, and rectal (per rectum). The parenteral routes of drug administration are subcutaneous, intramuscular, intravenous, intra-arterial, inhalations, subarachnoidal, intraperitoneal, and other.

A dose is the drug quantity which is administered to the patient. A word "dose" is of the Greek origin and in translation to English means a "portion". The following dose kinds are distinguished:

– single dose (*Dosis pro dosi*) is the drug quantity for the single perception;

– daily dose (*Dosis pro die*) is the drug quantity for a patient to take during a day;

– course dose (*Dosis pro curso*) is the drug quantity which is prescribed for full treatment course.

Drug Nomenclature. Elements of Latin Grammar

Each drug which is manufactured by different pharmaceutical plants has only one officially accepted name specified by Pharmacopoeia. But globally, the drug can have dozens of synonyms. For elimination of negative influence of this fact, the special expert commission of the World Health Organization works on creation of unified international unlicensed drug names. These drugs names may be used by any country.

Almost all drug names are nouns of an average sort of II declination (*Barbamylum*, *Validolum*). The names of acids are expressed by adjectives coordinated with a noun *Acidum*: *Acidum nicotinicum, Acidum boricum*.

Latin names of the salts are constructed according to the following principle: the cation name (alkaloid or metal) is tied to the first place and is expressed by a noun in Genitive case. The anion name is expressed by a noun in Nominative case (*Codeini phosphas*, *Morphini hydrochloridum*).

Anion name depends on its structure and is formed by adding different suffixes to the word root:

- -*idum* (Genitive case -*i*) – for salts of oxygen-free acids with inorganic basis (*Natrii chloridum*);
- prefix *hydro*- and suffix -*idum* are used in anion names of oxygen-free acid salts with inorganic bases (*Adrenalini hydrochloridum*);
- -*as* (Genitive case -*atis*) is used in anion names of oxygen-containing acids with maximal oxygen content (*arsenas, nitras, benzoas*);
- -*is* (Genitive case -*itis*) is used for salt anion of oxygen-containing acids with less oxygen content (*arsenis, nitris*).

Also, the following international Latin names are used: oxide – *oxidum*, peroxide – *peroxidum*, hydroxide – *hydroxidum*.

Other drug names and words used in prescription (names of medicinal forms and plants, etc.) are also written in corresponding case according to general rules of the Latin grammar.

In prescription, only one noun of IV declination is used – "*spiritus*", and only one noun – "*species*"– of V declination.

It is necessary to remember, that the prepositions "*in*" and "*cum*" require Instrumental case of noun which is written after them, and the expression "*ut fiat*" requires Nominative case of noun written after it.

The table of the words endings in cases which are most commonly used in prescriptions is given below.

Table 1 – Most commonly used words endings in prescriptions

Number	Case	Declination				
		I	II	III	IV	V
Singular	N.	*a*	*um, us*	*different endings*	*us*	*es*
	G.	*ae*	*i*	*is*	*us*	*ei*
	Acc.	*am*	*us*			
	Abl.	*a*	*o*			
Plural	N.	*ae*	*i, a*			
	G.	*arum*	*orum*			
	Acc.	*as*	*os, a*			
	Abl.	*is*	*is*			

Prescription: Structure and Registration Rules

A prescription is the written physician direction to the pharmacy about the drug preparation and its handing over to the patient with the indication of its usage mode. A prescription is important medical and juridical document. A doctor carries the juridical responsibility for correctness of drug prescriptions. When the drug is released for free, the prescription is also a financial document.

Prescriptions should be written only by pen (not by pencil). A doctor should fill all the stipulated columns in the prescription blank. After the last prescription, physician should put the signature and personal seal. Corrections are not permitted in the prescriptions. The prescribed treatment should be entered in an outpatient card of the patient.

The doctors have no right to prescribe the prescriptions of drugs, which are not permitted to application in the country, and at the patient's request without examining the patient and establishing diagnosis.

In English countries as well as in the countries where the training is carried out in English, the prescription is prescribed in English on the special form or on a paper sheet. The following structural elements should be specified in the prescription:

1 – surname and name of the doctor;

2 – license qualification of the doctor or his professional degree;
3 – address of the doctor;
4 – the doctor's office telephone number;
5 – date of registration of the prescription;
6 – surname and name of the patient;
7 – address of the patient.

The scheme of prescription blank which is used in English countries is given below. The order of prescription registration in English countries is the following.

A doctor writes the mark "R" in the right top corner, which means "*to take*". After that, the doctor writes the drug name with a capital letter in the Nominative case (8). In the same line, the doctor also indicates the drug dose (9) and its general amount for the treatment course (10).

In the right corner after "Sig." (11), physician writes the detailed instruction for the patient about the drug usage and the need for repeated drug prescription (12). Also, doctor writes information about the need of drug storage in the place which is inaccessible for children (13).

After that, a physician gives (14) the information about observance necessity of the certain rules of safety in drug reception (for example "It is prohibited to use alcohol", "Causes drowsiness", etc.). In the left corner below, doctor puts the signature (15), indicates the identification data (16), and the number of the license state registration (17).

1 JOHN B. DOE, M. D. 1234 SOUTH NORTHEAST DR. 3 WEST CITY, CA 94999 (234)555-6789 4		
FOR: 6	DATE: 5	
ADDRESS: 7		
R 8 9 (DRUG NAME AND STRENGTH) (QUANTITY) 10 Sig: 11		
REFILL TIMES		
OR UNTIL 12		
NO CHILDPROOF CONTAINER	13	
WARNING: 14	15 M. D.	
	ID 1234567 16 STATE LICENSE NO. 17	

In Ukraine, the prescription form contains the same important information. The following prescription structure is standard (Table 2).

Table 2 – The standard structure of prescription

№	Latin name of the prescription graph	Contained information
1	Inscriptio I	Medical institution stamp (its name, the address, a phone number, and a code) is in this inscription
2	Inscriptio II	This inscription includes the age category of the patient (child or adult) and date of registration of prescription
3	Nomen aegroti	Name and surname of the patient and his (or her) age
4	Nomen medici	Name and surname of the doctor who writes out this prescription
5	Invocatio s. praepositio	The reference of the doctor to the pharmacist with the request to manufacture and give out (or only to give out) a medicine to the patient: the word "take" written in Latin: "Recipe" (commonly it is written in abbreviated form "Rp.:")
6	Designatio materialum s. ordinatio	Name of medicinal remedy or the list of medicinal remedies included into the complex drug which will be manufactured in a drugstore
7	Subscriptio s. praescriptio	The doctor's instructions for a pharmacist about preparation of a certain medicinal form and its distribution in necessary quantities
8	Signature	It is the recommendation of the doctor for the patient about the manner of drug's use. In this part the following must be necessarily indicated: – the method of dosing: to accept 1 teaspoon; 1 ml; 2 tablets and so on; – the route of drug's administration: subcutaneously, intramuscularly, intravenously, perorally and so on; – frequency or time of the drug's reception (3 times per day, before meal, at headache, at bedtime)

A prescription is separated from the next prescription by short line. New prescription is started with an abbreviation "*Rp.*:". After the last prescription, doctor puts the signature.

A prescription of different medicinal forms can be short or full (unwrapped). A short variant is used basically for prescription of the officinal (ready-made) medicinal forms, and full – for the forms prepared in the drugstore. Nowadays, most drugs are manufactured by pharmaceutical industry. Therefore, they are prescribed only by short form. The examples of both short and full forms of prescriptions are given in the material about different medicinal forms.

Rules of Dosage. Measure of Weight and Volume

In modern medical practice, the drug doses are specified in decimal measurement system. A gram is the weight unit that is mass of 1 ml of distilled water at temperature 4 °C. In the prescription, it is designated as 1.0. The following sizes are used for the drug dosage: 0.1 – one decigram; 0.01 – one centigram; 0.001 – one milligram; 0.0001 – one decimilligram; 0.00001 – one centimilligram; 0.000001 – one microgram. It is necessary to remember, that dry substance quantities should be given in grams.

Liquid substance quantities are given in milliliters, grams or drops. Most commonly, quantity of liquid substance is given in milliliters (ml). If several drops of some substance are included in medicinal form, the quantity of drops is designated by the Roman digits, e. g.: "5 drops" – "*gt. V*" ("*gt.*" is abbreviation of a word "*guttas*" – "drops" in Instrumental case of plural).

Most Important Abbreviations Used in Prescription

Only abbreviations which do not cause confusion are permitted in prescriptions.

The list of abbreviations most commonly used in prescriptions is given below.

Table 3 – Most commonly used abbreviations in prescriptions

Used abbreviation	Meaning
āā – ana	fifty-fifty
Ac. – Acidum	acid
amp. – ampulla	ampoule
Aq. – Aqua	water
But. – Butyrum	oil (solid)
D. – Da	give out
D. t. d. – Da tales doses	give out such doses
S. – Signa	designate
dil. – dilutus	the dissolved
Emuls. – Emulsum	emulsion
Empl. – Emplastrum	plaster
Extr. – Extractum	extract
f. – fiat	it is formed
fol. – folium	leaf
in amp. – in ampoules	in ampoules
in caps. – in capsulis	in capsules
in tab. – in tabulettis	in tablets
Inf. – Infusum	infusion
Lin. – Linimentum	liniment
M. – Misce	admix
N. – numero	quantity
pulv. – Pulvis	powder
q. s. – quantum satis	how many it is required
rad. – radix	root
Rp. – Recipe	take
rhiz. – rhizoma	rootstock
S. – Signa	designate
sicc. – siccus (a, um)	dry
simpl. – simplex	simple
Sol. – Solutio	solution
Steril.! – Sterilisetur!	sterilize
supp. rect. (vag.) – suppositorium rectale (vaginale)	suppository rectal (vaginal)
Tinct., T-ra – tinctura	tincture
ung. – unguentum	ointment

Rules for the Prescription of Medicinal Forms

Solid Medicinal Forms

The solid medicinal forms are powders, tablets, dragee, granules and medicinal herb compositions.

Powders – *Pulveres (Pulv.)* (Nominative case, singular – *Pulvis*, Genitive case, singular – *Pulveris*)

Powder is a solid medicinal form used externally or internally. Different synthetic agents, medications of herbal and animal origin, and products of bacterial vital activity may be prescribed in form of powders.

In dependence of quantity of medicinal remedies, there are simple (containing only one remedy) and complex (containing two or more remedies) powders. Also, powders are divided into dosed (commonly used for peroral administration) and non-dosed (commonly used for external application) powders.

For peroral intake, only non-toxic agents may be prescribed as non-dosed powders. Patients take such powders either for one intake or for several perceptions dosing it by spoons (tea-spoons, dessert spoons, or table-spoons).

According to degree of grinding, there are coarse (*pulvis grossus*), fine (*pulvis subtilis*), and ultrafine (*pulvis subtilissimus*) powders. Substances, which are used in large quantity, are prescribed in form of coarse powders. Fine powders are prescribed for peroral intake. Smallest powders are used externally. For oral intake, the finer is the powder the faster it is dissolved and absorbed. For external use, ultrafine powder exhibits the marked mechanical influence and has high absorptive surface.

Powders for External Use

The finest powder (Lat. – "*pulvis subtilissimus*") for external use is called dusting powder (Lat. – "*Aspersio*"). This medicinal form is most commonly used for processing of injured part of skin. Dusting powders are prescribed as non-dosed powders. The weight of dusting powder is from 5 g to 100 g or more. Dusting powders are prescribed both in full and in short form. In dusting powders, the medicinal remedies are used either in pure state or in combination with indifferent substances which are used as excipients. Such substances as talc (*Talcum*), starch (*Amylum*) or zinc oxide (*Zinci oxydum*) are used as excipients. The dusting powders containing two or more medicinal remedies are prescribed only in full form.

The examples of prescription of dusting powders in full and in short forms are given below.

> *Prescribe both in full and in short forms of prescription 50 g of dusting powder which contains 5 % of anaesthesine (Anaesthesinum). Use for the patient's injured part of skin preparation.*

Full form of prescription. In the full form, a doctor should list all the ingredients of this medicinal form and indicate their weight in grams.

A calculation of anaesthesine's weight is the following. The total weight of dusting powder is 50 g. It is 100 %. Anaesthesin's weight is designated as ***x*** g; but it is known that is it 5 %. On the base of these data we make the following proportion:

$$50 \text{ g} \quad – \quad 100\ \%$$
$$x \text{ g} \quad – \quad 5\ \%$$

We find the necessary anaesthesin's weight as result of this proportion decision:

$$x = 50 \cdot 5 : 100 = 2.5 \text{ g}$$

That is, 2.5 g of anaesthesine should be taken. As excipient, any of possible substances may be used, e. g., starch. It is the starch weight calculation: 50 g – 2.5 g = 47.5 g.

A *full form* of prescription is the following:

Rp.: Anaesthesini 2.5
Amyli 47.5

M. f. pulv. subtilissimus

D. S. To use for the treatment of injured skin part.

An order of *short form* of prescription for this drug is the following:

Rp.: Aspersionis Anaesthesini 5 % – 50.0

D. S. To use for treatment of the injured skin part.

In a short form of prescription, the name of medicinal form is written after "*Rp.*:", after that – the medicinal substance name, its percentage, and total dusting powder weight. It is necessary to notice, that short prescription form is possible only in case when dusting powder consists of two substances: medicinal remedy and excipient.

Sometimes, medicinal remedy is used in dusting powders in pure form without excipients.

Prescribe 30 g of anaesthesine in dusting powder. To use for treatment of the injured skin part.

Rp.: Anaesthesini subtilissimi 30.0

D. S. to use for treatment of the injured skin part.

Powders for Internal Use

Powders for internal use may be both simple (consist of one medicinal remedy) and complex (consist of two or more medicinal remedies). Powders for internal use are prescribed with indication of single doses of medicinal remedies and general amount of powders. A powder weight should be within the range from 0.1 g to 1.0 g. If total weight of medicinal remedies in one powder is less than 0.1 g (or 0.05 g for herbal powders), the indifferent substance should be added to such powder (sugar (*Saccharum*) or glucose (*Glucosum*)). The optimal weight of dosed powder is 0.3–0.5 g.

The examples of dosed powders for internal use are given below.

Prescribe 20 powders of calcium gluconate (Calcii gluconas, the single dose is 0.5 g) for oral intake 3 times a day.

Rp.: Calcii gluconatis 0.5

D. t. d. N. 20

S. Orally 1 powder 3 times a day.

Prescribe 10 powders of papaverine hydrochloride (Papaverini hydrochloridum, the single dose is 0.02 g) for oral intake twice a day.

Rp.: Papaverini hydrochloridi 0.02
Sacchari 0.3
M. f. pulv.
D. t. d. N. 10
S. Orally 1 powder twice a day.

Prescribe 10 powders containing platyphyline hydrotartrate (Platyphyllini hydrotartras, single dose is 0.003 g) and papaverine hydrochloride (Papaverini hydrochloridum, single dose is 0.03 g) for oral intake 3 times a day.

Rp.: Platyphyllini hydrotartratis 0.003
Papaverini hydrochloridi 0.03
Sacchari 0.3
M. f. pulv.
D. t. d. N. 10
S. Orally 1 powder 3 times a day.

Capsules – *Capsulae* (*Caps.*)
(Nominative case, singular – *Capsula*; Instrumental case, plural – *Capsulis*)

Medicinal remedies having unpleasant smell or taste, or irritating the mucosa are taken up in the capsules. Capsules are membrane cases for oral intake containing dosed powders, granules, pasty or liquid medicinal remedies.

There are starch capsules or cachets (*Capsulae amylaceae seu oblatae*) and gelatin capsules (*Capsulae gelatinosae*). Presently, gelatin capsules are mainly used.

Capsules are prescribed according to the following rules:

1. Medicinal remedy weight is given after its name.

2. Independently of the drug dose, indifferent substances are not added to medicinal remedy.

3. After "*D. t. d. N....*", the indication on the issuing of the drug in capsules is necessary.

4. If the drug dose is higher than quantity of the drug in a capsule, several capsules are prescribed for each intake.

The order in which the capsules are prescribed is as follows:

Prescribe 12 capsules, each contains 0.05 g of Doxycycline hydrochloride (Doxycyclini hydrochloridum, the single dose is 0.1 g). Take orally once a day.

Rp.: Doxycyclini hydrochloridi 0.05

D. t. d. N. 12 in caps.

S. Take orally 2 capsules once a day.

Microcapsules are microscopic particles of medicinal remedies which are put into cachets. Particles with size from 100 to 500 μm are most commonly used in medicine. Particles with size 1 μm and less are called nanocapsules. Microcapsulation enables to protect the medicinal remedies (vitamins, antibiotics, nitroglycerin, enzymes, vaccine, etc.) from the influence of external environment and is used to mask undesirable taste. Microcapsules provide the release of medicinal remedy in the necessary part of gastrointestinal tract (enteric-soluble microcapsules) and prolong the drug action (spansules). Due to the usage of separating coatings, microcapsules make possible the combination of inconsistent substances in one capsule. Also, microcapsulation is used for transformation of liquids in pseudo-solid state (microcapsules filled with liquid medicinal remedies).

Presently, a variety of drugs is manufactured in microcapsules. Microcapsulated drugs are also manufactured in tablets, suspensions, spansules, and rectal capsules. Spansules are solid gelatin capsules containing certain quantity of granules, microdragee, or microcapsules of medicinal remedies. There are investigations about a possibility of the microcapsules use in injections, eye drops, and tablets for implantation. The patches with deposited thin layer of microcapsulated medicinal remedies are of particular interest.

Tablets – *Tabulettae* (*Tab.*)
(Nominative case, singular – *Tabuletta*; Genetive case, singular – *Tabulettae*; Genetive case, plural – *Tabulettarum*; Instrumental case, plural – *in tabulettis*)

Tablet is the dosed solid medicinal form produced by the pharmaceutical industry by means of components pressing. As a rule, tablets are used for oral administration, but some tablets are used sublingually (nitroglycerin, methyltestosterone), or for implantation (Esperal). Also, tablets are sometimes used for preparation of solutions for external use (furacilinum).

Tablets are comfortable medicinal form. Their advantages over powders consist in the following:

– tablets are better stored because protected from influence of light, air, and moisture;

– tablets mask the undesirable taste of remedies;

– tablets prevent the undesirable influence of medicinal remedies upon the tooth enamel;

– multilayer tablets provide the consistent absorption of several medicinal remedies and ensure the prolonged drug action.

Negative influence of tablets is the following:

– in some cases, tablets (sodium bromide, potassium bromide) can cause mechanical or chemical irritation of esophageal and gastric mucosa;

– due to improper storage, tablets can lose the ability to break up in gastrointestinal tract;

– due to prolonged tablets storage, medicinal remedies can undergo chemical transformation.

Tableted drugs act more slowly than corresponding powders because tablets should be initially broken up and only after this undergo the dissolution and absorption. Tablets are not prescribed for children, seriously sick in unconscious state, and for persons who cannot swallow tablets due to different causes.

Tablets consist of medicinal remedies, excipients, and thinners. The following substances are used as excipients: lactose, starch, glucose, sodium hydrocarbonate, sodium chloride, calcium phosphate,

acetylcellulose, talc, cocoa, etc. Total quantity of excipients should be not more than 20 % of summary mass of thinners and medicinal remedies. Thinners are used for formation of tablets with necessary weight in cases when dose of remedies is very small.

Tablets for external use containing poisoning substances are respectively colored. For example, tablets containing mercuric chloride (corrosive sublimate) are colored by eosin, all other poisoning tablets – by methylene blue.

Tablets which are stored during prolonged time should be tested for disintegration before their usage.

Tablet weight is within 0.1–2 g. Average tablet mass is 0.3–0.5 g.

The following information should be given in prescriptions of tablets: information about drug product (manufactured by pharmaceutical industry form), general quantity of prescribed tablets, single dose of a drug, and mode of drug usage.

If the drug single dose is more than contained in one tablet, the necessary quantity of tablets is prescribed for each intake. In cases when single dose of the drug is less than contained in one tablet, the necessary part of one tablet is prescribed.

The tablets are prescribed only with the short form of prescription. Magistral (full) form of prescription of tablets does not exist.

Prescribe 100 tablets containing 0.3 g of isoniazid (Isoniazidum, the single dose is 0.3 g) for oral intake 3 times a day.

Rp.: Tab. Isoniazidi 0.3 N. 100

D. S. Take 1 tablet orally 3 times a day.

Also, the following variants of this prescription are possible:

Rp.: Isoniazidi 0.3

D. t. d. N. 100 in tab.

S. Perorally 1 tablet 3 times per day.

Or:

Rp.: Tab. Isoniazidi 0.3

D. t. d. N. 100

S. Perorally 1 tablet 3 times per day.

A doctor can use any of these forms in prescriptions.

Prescribe 20 tablets, each contains 0.0001 g of Digitoxine (Digitoxinum, the single dose is 0.00005 g) for oral intake once a day.

Calculation of the tablet part for one intake:

0.00005 : 0.0001 = 0.5 tablet.

Rp.: Digitoxini 0.0001
D. t. d. N. 20 in tab.
S. ½ tablet orally once a day.

Rp.: Tab. Digitoxini 0.0001
D. t. d. N. 20 in tab.
S. ½ tablet orally once a day.

Rp.: Tab. Digitoxini N. 20
D. S. ½ tablet orally once a day.

The following structure of prescription is used for tablets having special name and containing several medicinal remedies (e. g., "*Aeron*", "*Allocholum*", etc.).

Prescribe 30 tablets of "Allocholum" (the single dose is one tablet) for oral intake 3 times a day before meal.

Rp.: Tab. "Allocholum" N. 30
D. S. Use 1 tablet orally 3 times a day before meal.

Dragée (*Dragee*)
(Genetive case, singular – *Dragee*; Instrumental case, singular – *Dragee*)

Dragée is solid dosed medicinal form for internal use, manufactured by the pharmaceutical industry by repeated overlay of medicinal remedies and excipients around the sugar pellet. The following substances are used in dragée as excipients: sugar, magnesium carbonate starch, talc, cacao, wheat flour, etc. For protection of medicinal remedies from action of gastric juice, dragées are covered by special coating dissolved in basic environment of intestine. Weight of a dragée is from 0.1 g to 0.5 g, but not more than 1 g. After oral intake, dragée is dissolved for 30 minutes.

A form of dragée prescription is like the form of tablets prescription.

Prescribe 30 dragées containing 0.025 g of propazine (Propazinum, the single dose is 0.05 g). Take orally 2 times a day after meal.

Rp.: Dragée Propazini 0.025 N. 30
D. S. 2 dragées orally 2 times a day after meal.

Rp.: Propazini 0.025
D. t. d. N. 30 in dragée
S. 2 dragées orally 2 times a day after meal.

Rp.: Dragée Propazini 0.025
D. t. d. N. 30
S. 2 dragées orally 2 times a day after meal.

Prescribe 30 dragées Undevitum (single dose is 1 dragee) for oral intake 2 times a day.

Rp.: Dragée Undeviti N. 30
D.S. 1 dragee orally 2 times a day.

Some medicines are manufactured in the form of microdragée that provides prolongation of their action. Microdragées are formed by applying of medicinal remedies and sugar syrup (used as glue) around the fine sugar grains. The presence or absence of the coating around microdragée defines the time of the medicinal remedies absorption.

Eye Membranes – *Membranulae ophthalmicae*

(Nominative case, singular – *Membranulae ophthalmicae, s. Lamellae,* Instrumental case, singular – *Membranulas ophthalmicas, s. Lamellas*)

The eye membranes are sterile polymeric plates with the size of 9×4.5×0.35 mm, which contain medicinal remedies in definite doses and are dissolved in lacrimal fluid. The eye membranes can be stored in hermetically closed containers nearly 1 year.

After applying on the eye conjunctive, the dissolution of polymer is beginning.

In case of using the eye membrane, the therapeutic concentration of medicinal remedy can be maintained for 24 hours.

In comparison with eye drops, the eye membranes have the following advantages:

– the support of stable therapeutic concentration of medicinal remedy during long period of time;

– the high stability of medicinal form;

– the maintenance of sterility during significant period;

– more exact dosage of a drug.

Nowadays in medical practice the eye membranes (Membranulae ophthalmicae) with pilocarpine hydrochloride, atropine sulphate, neomycine sulphate, and other medicines are used.

The eye membranes are prescribed with short form.

Prescribe 30 eye membranes containing pilocarpine hydrochloride (Membranulae ophthalmicae cum Pilocarpini hydrochlorido). Use one membrane for the side of a lower eyelid 1 time daily.

Rp.: Membranulas ophthalmicas cum Pilocarpini hydrochlorido N. 30
D. S. Use one membrane for the side of a lower eyelid 1 time daily.

Hometasks for Prescription

1. Prescribe both in short and in full form 40 g of powder for external use containing 2 % of salicylic acid (*Acidum salicylicum*). Use for treatment of the injured part of skin.

2. Prescribe 20 powders of nicotinic acid (*Acidum nicotinicum*, single dose is 0.03 g) for oral intake 3 times a day.

3. Prescribe 30 powders of platyphyllin (*Platyphyllini hydrotartras*, single dose is 0.003 g). Take orally twice a day.

4. Prescribe 10 powders of Aspirin (*Aspirinum*, single dose is 0.25 g) for oral intake at headache.

5. Prescribe 30 capsules containing 0.15 g of rifampicine (*Rifampicinum*, single dose is 0.3 g) for oral intake 2 times a day.

6. Prescribe 50 tablets of dexamethasone (*Dexamethasonum*, single dose is 0.0005 g). The drug product: tablets, containing 0.0005 g of dexamethasone. Take orally 3 times a day.

7. Prescribe 30 tablets of mellictinum (Mellictinum, the single dose is 0.02 g) for oral intake 3 times a day. Drug product: tablets containing 0.02 g of mellictinum.

8. Prescribe 20 tablets of "*Bellataminalum*" (single dose is one tablet). Take orally 3 times a day.

9. Prescribe diazolin (*Diazolinum*, the single dose is 0.05 g). The drug product: dragee, containing 0.05 g of diazolin. Take orally 3 times a day.

10. Prescribe nimodipine for oral intake 2 times a day (*Nimodipinum*, the single dose is 0.06 g). The drug product: tablets containing 0.03 g of nimodipine.

11. Prescribe picamilon for oral intake 3 times a day (*Picamilonum*, the single dose is 0.02 g). The drug product: tablets containing 0.02 g of picamilon.

12. Prescribe 20 commercial tablets of "*Nacom*" for oral intake 2 times a day (the single dose is ½ tablet).

Soft Medicinal Forms

The soft medicinal forms are ointments, pastes, liniments (or liquid ointments), suppositories, plasters, and creams.

Ointments – *Unguenta* (Ung.)
(Nominative case, singular – *Unguentum;* Genitive case, singular – *Unguenti)*

Ointment is soft non-dosage complex medicinal form with viscous homogeneous consistency for external use.

Ointments are prepared by mixing various medicinal substances with the form-building substances, which are called ointment bases. Ointments form an equal film (which does not slip) on the skin or mucosa surface. Antibiotics, hormones, heavy metal salts, astringing,

irritating and other substances are used as medicinal remedies in ointments.

Animal or vegetable fats and oils, their derivatives, fat-like substances, carbohydrates, and other substances are used as ointment bases. Lanolin and vaseline are most frequently used among them. The base for ointment should be indifferent, mix well with remedy and easily give back, remain constant under the influence of light or heat, do not interact with medicinal substances, and thaw at body temperature. The base for eye ointment should be also sterile and neutral.

The amount of prescribed ointment depends on a way of its use. The eye ointments are prescribed in amount of 5–10 grams, ointments for lips and nose – in amount of 10–20 grams, for application on injured parts of the skin – 15–100 grams and more.

Ointments are non-dosed medicinal forms. Therefore, the amount of ointment in a prescription is prescribed as a total unit. Simple ointments consist of two ingredients: one active and one inert substance. Complex ointments consist of more than two ingredients.

The percentage of powder-like substances in ointment should be no more than 25 %. Otherwise, ointment turns to paste. Ointments are prescribed both in short and in full form of prescription. Most ointments are prescribed in a short form.

In the short form of prescription, the amount of active substance is given in percent or in mass units. The short form of prescription begins with the word "*Unguenti*" ("*Ung.*"). After that the name of medicinal remedy is written, its concentration in percents, and general amount of ointment.

In the full form of the prescription, the names of all ingredients of this ointment are listed. The weight of substance is indicated after the substance name. Also, the indication about preparation of ointment from these components is given ("*M. f. ung.*").

Prescribe 50 g of ointment based on vaseline (Vaselinum) which contains 1 % of tetracycline hydrochloride (Tetracyclinum hydrochloridum). To use for application on the injured parts of skin.

Rp.: Ung. Tetracyclini hydrochloridi 1 % – 50.0
D. S. To use for application on the injured parts of skin.

The following is a full form of this prescription:

Rp.: Tetracyclini hydrochloridi 0.5
Vaselini 49.5
M. f. ung.
D. S. To use for application on the injured parts of skin.

The ointments are widely used in ophthalmology. Slowly developing effect is the feature of eye ointments. In comparison with eye drops, the duration of eye ointments action is longer. The indication "*Eye ointment*" should be written in a signature before the indication about the mode of its use.

Prescribe 10 g of eye ointment with 2 % of polymyxine M sulfate (Polymyxinum M sulfas). To put behind a lower eyelid 4 times daily.

Rp.: Ung. Polymyxini M sulfatis 2 % – 10.0
D. S. Eye ointment. To put behind a lower eyelid 4 times daily.

Example of prescription for ointment, containing medicinal remedy the activity of which is expressed in action units, is given below.

Prescribe both in short and in full form 50 g of ointment, each gram of which contains 10 000 of international units (IU) of erythromycine (Erythromycinum). Use for application on the injured parts of skin.

The full form:

Rp.: Erythromycini 500 000 IU
Vaselini 50.0
M. f. ung.
D. S. Use for application on the injured parts of skin.

The short form:

Rp.: Ung Erythromycini 50.0 (1,0 – 10,000 IU)
D. S. Use for application on the injured parts of skin.

Pastes – *Pastae*
(Nominative case, singular – *Pasta;* Genitive case, singular – *Pastae*)

The paste is non-dosed medicinal form. Paste is thick ointment containing dry substances in amount from 25 to 65 %. Due to thicker consistency, paste can remain on the body surface during longer time than ointment. The pastes have adsorbing, drying and anti-inflammatory properties. As a rule, the pastes are used for applying on purulent and wet surfaces, e. g., for eczema.

Paste consists of medicinal remedy (remedies) and basis. Substances used as basis for pastes are the same as for ointments. If amount of medicinal remedies in paste is less than 25 %, one or more inert powders (starch (*Amylum*), talc (*Talcum*), zinc oxide (*Zinci oxidum*), white clay (*Bolus alba*)) should be added. In the prescription, inert powders are indicated before bases.

There are officinal and magistral pastes. The magistral paste is prescribed only in full form of prescription. The paste prescription is like the ointment, only the word "*Unguenti*" is replaced by a word "*Pastae*".

Prescribe 50 g of paste based on vaseline, which contains 5 % anaesthesine (Anaesthesinum). Use for application on the injured parts of skin.

Rp.: Anaesthesini 2.5
Talci 10.0
Vaselini ad 50.0
M. f. pasta
D. S. Apply on the injured parts of skin.

Because amount of anaesthesine is 5 %, we should add talc for paste formation. Minimum amount of talc is 20 % that is equal to 10 g.

Note. The word *"ad"* before weight of vaseline means *"up to"* ("up to total weight of paste"). This word is used in full forms of prescription for both ointments and pastes when the percentage of dry substances is more than 5 %.

Prescribe 40 g of paste containing 3 % of salicylic acid (Acidum salicylicum), 2 % of boric acid (Acidum Boricum), and 10 % of zinc oxide (Zincum oxydum). Apply on the injured parts of skin in the morning and in the evening.

Rp.: Acidi salicylici 1.2
Acidi borici 0.8
Zinci oxydi 4.0
Talci 12.0
Vaselini ad 40.0
M. f. pasta
D. S. Apply on the injured parts of skin, morning and evening.

In this case, the quantity of dry powders equals 15 %. Therefore, for paste formation it is necessary to add talc. 12 g of added talc is 30 % of the total amount of paste.

Thus, the prescribed paste contains 45 % of dry substances.

The officinal pastes are prescribed only with a short form.

Prescribe 100 g of zinc-salicylic paste (Pasta Zinci-salicylata). Use for application on the injured parts of skin.

Rp.: Pastae Zinci-salicylatae 100.0
D. S. Apply on the injured parts of skin.

This paste also may be prescribed as Lassar's paste:

Rp.: Pastae Lassari 100.0
D. S. Apply on the injured parts of skin.

Lassar's paste composition is the following:

- Acidum salicylicum – 2.0;
- Zinci oxidum – 25.0;
- Amylum – 25.0;
- Vaselinum – 48.0.

Suppositories – *Suppositoria* (*Supp.*)
(Nominative case of singular – *Suppositorium*;
Genitive case of singular – *Suppositorii*;
Dative case of singular – *Suppositorium*;
Dative case of plural – *Suppositoria*)

Suppository is the soft dosed medicinal form which stays in a firm condition at room temperature and thaws at body temperature. The suppositories are divided into rectal (administered into the rectum) and vaginal (administered into the vagina) ones.

In comparison with oral drug intake, medicinal substances are soaked up faster from the rectum. Rectally administered drugs are not destroyed by enzymes of gastrointestinal tract. These drugs are not exposed to primary passage through the liver and do not show unpleasant taste and smell. In certain cases, the rectal form can replace the form for injection.

Suppositories consist of medicinal substances and basis. The basis should be indifferent, it should not irritate mucous, poorly soak up through mucous, and to be steady at a storage. Most often used basis in suppositories are:

– cocoa oil obtained from cocoa seeds (melting temperature is 30–34 °C);

– butyrol – mixture of hydrogenated fats with melting temperature 35–36 °C;

– gelatin-glycerol mass containing 1 part of gelatin, 5 parts of glycerol, and 2 parts of water.

If the basis is not specified in the prescription, a pharmacist uses cocoa oil as basis for suppositories.

Rectal suppositories are used both for local and systemic action. Vaginal suppositories are used basically for local action.

Weight of rectal suppositories is 1.1–4 g, weight of vaginal suppositories is 1.5–6 g. If suppository weight is not specified in the prescription, rectal suppositories are made with weight of 3 g, and vaginal – 4 g.

The suppositories are prescribed in both short and in full forms. In the full form of prescription, a quantity of the basis can be not

specified. Instead, we can indicate "*quantum satis*" – "as much as necessary".

Prescribe 6 rectal suppositories containing 0.2 g of euphylline (Euphyllinum). Use 1 suppository into the rectum twice a day.

Rp.: Euphyllini 0.2
Butyri Cacao 2.8
M. f. supp. rect.
D. t. d. N. 6
S. Use 1 suppository rectally 2 times a day.

Or:

Rp.: Euphyllini 0.2
Butyri Cacao q.s.
ut f. supp. rect.
D. t. d. N. 6
S. One suppository rectally 2 times a day.

Prescriptions of vaginal suppositories are like the rectal ones. Only the words "*supp. vag.*" should be indicated instead "*supp. rect.*".

Prescribe 12 vaginal suppositories containing 0.2 g of ichthyol (Ichthyolum). Use 1 suppository into the vagina 2 times a day.

Rp.: Ichthyoli 0.2
Butyri Cacao 4.0
M. f. supp. vag.
D. t. d. N. 12
S. Use 1 suppository in vagina twice a day.

Or:

Rp.: Ichthyoli 0.2
Butyri Cacao q.s.
ut. f. supp. vag.
D. t. d. N. 12
S. Use 1 suppository in vagina 2 times a day.

Presently, most suppositories are manufactured by the pharmaceutical industry. Such suppositories are prescribed only in

short form. The prescription is begun from the indication of the medicinal form (*Supp*.). After that the conjunction "*cum*" ("with") is written and the name of medicinal substance in an instrumental case with its dose. In the next line we indicate "*D. t. d. N.*" and then make out the signature.

Prescribe 10 officinal rectal suppositories containing 0.1 g of anaesthesine. Use 1 suppository rectally for pain relief.

Rp.: Supp. cum Anaesthesino 0.1
D. t. d. N. 10
S. Use 1 suppository rectally at pains.

There are suppositories having the commercial names. For example, "*Bethiolum*", "*Anusol*" and others. Such suppositories are prescribed only in short form without conjunction "*cum*".

Prescribe 10 vaginal suppositories "Osarbonum". Use one suppository into vagina in the evening.

Rp.: Supp. "Osarbonum" N. 10
D. S. Use 1 suppository into vagina in the evening.

Hometasks for Prescription

1. Prescribe both in short and full forms of prescription 50 g of ointment containing 0.5 % of neomycin sulfate *(Neomycinum sulfas)*. To use for application on the injured parts of skin.

2. Prescribe 2.5 g of eye ointment with 0.5 % of hydrocortisone *(Hydrocortisonum*). To put behind the lower eyelid in the morning and in the evening.

3. Prescribe 10 g of sulfuric ointment (*Unguventum sulfuratum*). To use for application on the injured parts of skin 3 times a day.

4. Prescribe both in short and full forms 50 g of ointment containing 15 000 international units (IU) of mycoheptin *(Mycoheptinum)* in each gram. To use for application on the injured parts of skin.

5. Prescribe 10 g of ointment containing 0.3 g of salicylic acid *(Acidum salicylicum)* and 0.6 g of benzoic acid *(Acidum benzoicum)*. To use for application on the injured parts of skin.

6. Prescribe 10 g of officinal eye ointment with erythromycin *(Erytromycinum)*. To put behind the lower eyelid 4 times a day.

7. Prescribe 10 g of paste containing 5 % of resorcinol *(Resorcinum)*. To use for application on the injured parts of skin.

8. Prescribe 40 g of paste containing 3 % of salicylic acid (*Acidum salicylicum)*, 2 % of boric acid (*Acidum boricum)*, and 10 % of zinc oxide (*Zincum oxidum)*. To use for application on the injured parts of skin in the morning and in the evening.

9. Prescribe 30 g of paste containing 10 % of anaesthesine (*Anaesthesinum)* and 4 % of iodoform (*Iodoformium)*. To use for application on the injured parts of skin once a day.

10. Prescribe 30 g of officinal paste with *gramicidin* (*Pasta Gramicidini*). To put bandage with paste on the wound 1 time for two days.

11. Prescribe both in short and full forms 10 vaginal suppositories, each contains 0.5 g of trichomonacid (*Trichomonacidum)*. To use 1 suppository into the vagina in the evening.

12. Prescribe 20 vaginal suppositories, each contains 0.5 g of metronidazole *(Metronidasolum)*. To use 1 suppository into vagina in the evening.

13. Prescribe 10 officinal rectal suppositories, each contains 0.5 g of levomycetin (*Laevomycetinum)*. To use 1 suppository rectally 3 times a day.

14. Prescribe 20 officinal rectal suppositories "*Bethiolum*". To use 1 suppository rectally 2 times a day.

Liquid Medicinal Forms

Liquid medicinal forms include such forms as solutions, suspensions, emulsions, infusions, broths, liquid extracts, mixtures, tinctures, and some others.

Solutions – *Solutiones* (*Sol.*)
(Nominative case, singular – *Solutio*; Genetive case, singular – *Solutionis*)

Solutions are divided into solutions for external use, solutions for internal use, and solutions for parenteral (intravenous, intramuscular, etc.) administration.

Solutions for External Use

Solutions for external use are non-dosed medicinal forms. For prescribing these solutions it is necessary to know the concentration and general amount of solution (volume). Distilled water (*Aqua destillata*), ethyl alcohol (*Spiritus aethylicus*), glycerol (*Glycerinum*), or different liquid oils are used as solvents. Accordingly, solutions are divided into water, alcoholic (in Latin – *spirituosae*), and oil (in Latin – *oleosae*) solutions.

Volume of solution for external use depends on the mode of its use. Such medicinal forms as eye drops, ear drops, and nasal drops are prescribed in volume 5–10 ml. Solutions for washing of wounds, skin or for rinsing are prescribed in volume 50–500 ml. Solutions for gastric lavage and disinfection are prescribed in amount 1–2 L.

Certain examples of prescription of solutions for external use are given bellow.

Prescribe 200 ml of 0.02 % furaciline (Furacilinum) solution for bathing of wounds.

The general scheme of short form of prescriptions for external use is following: you indicate the name of medicinal form, next – the name of medicinal remedy and its percentage, and after dash – volume of the solution.

Rp.: Sol. Furacilini 0.02 % – 200 ml
D. S. Use for bathing of wounds.

Eye drops (*guttae ophtalmicae*) are water or oil solutions of medicinal remedy (or several remedies) used for application in the eye conjunctiva. The eye drops should be sterile and isotonic to lacrimal fluid. Water for injections, peach-kernel oil, or sweet-almond oil are used as dissolvent in the eye drops. The eye drops are prescribed both in full and short forms of the prescription. Doctor should indicate in signature "*Eye drops*" that confirms its sterility. After this, the doctor describes the mode of drug use.

Prescribe eye drops containing 0.3 % of zinc sulfate (Zinci sulfas) and 2 % of boric acid (Acidum boricum). Instill 1–2 drops into each eye 3 times a day.

Rp.: Zinci sulfatis 0.03
Acidi borici 0.2
Aquae pro injectionibus 10 ml
M. D. S. Eye drops. Instill 1–2 drops into each eye 3 times a day.

The volume of medicine is given according to the above-stated rule (10 ml). Because the percentage of zinc sulfate is 0.3 % (that is 0.3 g of substance is contained in 100 ml of solution), 0.03 g of zinc sulfate should be taken:

0.3 g – in 100 ml;
x – in 10 ml;
$x = 0.3 \cdot 10 : 100 = 0.03$ (g).

A calculation for boric acid is the following:

2.0 g – in 100 ml;
x – in 10 ml;
$x = 2.0 \cdot 10 : 100 = 0.2$ (g).

Prescribe eye drops containing 1 % of pilocarpine hydrochloride (Pilocarpini hydrochloridum). Instill 2 drops into each eye 3 times a day.

Rp.: Sol. Pilocarpini hydrochloridi 1 % – 5 ml

D. S. Eye drops. Instill 2 drops into each eye 3 times a day.

The example of prescription of nasal drops is given below.

Prescribe 1 % solution of Ephedrine hydrochloride (Ephedrini hydrochloridum). Instill 3 drops into the nose 3 times a day.

Rp.: Sol. Ephedrini hydrochloridi 1 % – 10 ml
D. S. Instill 3 drops into the nose 3 times a day.

Solutions for Oral Intake

Solutions for oral intake are dosed with a medicine glass, spoon (tablespoon, dessert spoon, or teaspoon), or drops.

It is necessary to remember that 1 tablespoon contains 15 ml, 1 dessert spoon – 10 ml, and 1 teaspoon – 5 ml. One ml of water solution contains 20 drops, one ml of alcoholic solution contains 50 drops, and one ml of oil solution contains 40 drops. It is most rationally to prescribe the solutions, which are dosed in drops, in amount of 10–20 drops for 1 intake.

Traditionally, the solution is dosed with drops if single dose of medicinal remedy is less than 0.05 g. If a single dose of medicinal remedy equals 0.05 g or more, its solution is dosed with tablespoons (for adults).

Solutions for oral intake are prescribed for 10–30 intakes.

Solutions for oral intake may be prescribed both in full and in short forms of prescriptions.

The examples of solutions, which are dosed by tablespoon and drops, are given below.

Prescribe solution of calcium gluconate (Calcium gluconas, single dose is 0.5 g) for oral intake 3 times a day.

A course of necessary reasoning is the following.

1. First, it is necessary to determine the measure which should be used for dosing the solution. In this case, the single dose is more than 0.05 g. Therefore, this solution is dosed by tablespoons (1 tablespoon contains 15 ml).

2. The next step is to determine the number of intakes. Let's prescribe this drug for 10 intakes.

3. Now we have enough information for calculation of solution volume and concentration:

– for 1 intake patient takes 1 tablespoon or 15 ml of solution. Therefore, for 10 intakes it is necessary to prescribe 150 ml of solution;

– calculation of percentage concentration for this solution: 0.5 g is contained in 15 ml; ***x*** g is contained in 100 ml. Decide the proportion: 0.5 · 100 : 15 = 3.3 %. That is, the concentration of this solution is 3.3 %.

Now we have all the necessary data for this prescription.

Rp.: Sol. Calcii gluconatis 3.3 % – 150 ml
D. S. Take orally 1 tablespoon 3 times a day.

Prescribe solution of promedol (Promedolum, the single dose is 0.02 g) for oral intake once a day.

Because the single dose is less than 0.05 g, this solution is dosed in drops. Let's prescribe 10 drops for 1 intake and total quantity of receptions is 20. Because 10 drops are 0.5 ml, the total volume of this solution is 10 ml (0.5 ml · 20 receptions = 10 ml).

The total amount of promedol is 0.4 g:

0.02 g (single dose) · 20 (amount of intakes) = 0.4 g.

Now we have all the necessary information for the full form of prescription:

Rp.: Promedoli 0.4
Aq. destill. 10 ml
M. D. S. 10 drops orally once a day.

Pay your attention that "*M. f. sol*." is not written.

For a short form of this prescription, we should calculate the percentage concentration of promedol in solution: 0.4 g · 100 : 10 = 4 %.

Rp.: Sol. Promedoli 4 % – 10 ml
D. S. 10 drops orally once a day.

Solutions for Injections

Injection is a medicinal form, used for parenteral administration. Water and oil solutions, sometimes – suspensions, emulsions, sterile powders or tablets (which should be dissolved directly prior to administration) may be administered parenterally.

Parenteral routes of drug administration are subcutaneous, intramuscular, intravenous, intra-arterial, etc. Most commonly, the following volumes are administered parenterally: 1–2 ml – subcutaneously, 3–5 ml – intramuscularly, 5–10 ml (or more) – intravenously. But sometimes there are exceptions.

The water solutions are more often used for subcutaneous administration. The water or oil solutions and suspensions are used for intramuscular administration. For intravenous administration, the water solutions are used. Solutions for parenteral administration must be sterile.

The term "*infusion*" is frequently used alongside with the term "*injection*". The distinction between them is following: relatively small volume of solution is administered in injection; but in infusion, the large volume of solution is administered.

Presently, injection solutions are manufactured by the pharmaceutical industry. But sometimes these solutions may be prepared by pharmacists.

In this material, the prescription rules only for ready-made injection forms are considered.

The pharmaceutical industry manufactures injection forms both in ampoules and in vials.

The prescription rules for ampoules are the following. As a rule, the volume of ampoule is in a range from 1 to 100 ml. Ampoules are the dosed medicinal forms. But the single dose may vary from an amount of drug in an ampoule. Therefore, it is necessary to calculate the amount (or volume) of a drug for 1 administration. The quantity of ampoules which are prescribed to a patient depends on the duration of treatment. As a rule, 5–10 ampoules are prescribed, sometimes – 20–50 ones.

Ampoules are prescribed only with the short form of prescription. After abbreviation "*Rp*.:" it is necessary to indicate the liquid form which is in an ampoule (for example: "*Sol*." or "*Susp*."). Sometimes the sterile powder is in ampoules. After that you write the name of the medicinal remedy, its percentage concentration, and the volume of solution in one ampoule (for liquid form) or weight of remedy in one ampoule (for sterile powder). In the next line you indicate "*D. t. d. N. 10* (or other amount) *in amp.".* The next line is "*Signa*".

Certain examples of ampoule prescriptions are given below.

Prescribe solution of ephedrine hydrochloride (Ephedrini hydrochloridum, the single dose is 0.1 g) for subcutaneous administration once a day. The drug product: ampoules containing 1 ml of 5 % ephedrine hydrochloride solution.

Rp.: Sol. Ephedrini hydrochloridi 5 % – 1 ml
D. t. d. N. 10 in amp.
S. 2 ml subcutaneously once a day.

It is known that 0.05 g of ephedrine hydrochloride is contained in 1 ml of 5 % solution. The single dose (0.01 g) is contained in 2 ml of this solution. Therefore, 2 ml of solution are administered.

The ampouled solutions may be officinal or novogalenic and have special commercial name. In such cases, only the drug name and its amount in ampoule is specified in prescriptions. The concentration and word "*Sol*." are not written.

Prescribe cordiamin (Cordiaminum, the single dose is 1 ml) for subcutaneous administration 3 times a day. The drug product: ampoules containing 1 ml of the drug.

Rp.: Cordiamini 1 ml
D. t. d. N. 10 in amp.
S. Administer 1 ml subcutaneously 3 times a day.

The powder-like substances, water solutions of which are destroyed during storage, also may be produced in ampoules. Such powder is dissolved directly before administration. Relevant information about this should be given in "*Signa*".

Prescribe hexenal (Hexenalum, the single dose is 0.5 g) for intravenous administration. The drug product: ampoules containing 1 g of dry substance.

Rp.: Hexenali 1.0
D. t. d. N. 10 in amp.
S. Dissolve the substance of one ampoule in 20 ml of sterile water. Administer 10 ml intravenously.

Besides ampoules, the drugs for parenteral administration are manufactured in vials. Unlike ampoules, the word "vial" is not written in their prescriptions.

Prescribe 20 vials containing 500 000 IU of dry benzylpenicillin sodium (Benzylpenicillinum natrium, the single dose is 250 000 IU). Administer intramuscularly 4 times a day.

Rp.: Benzylpenicillini natrii 500 000 IU
D. t. d. N. 20
S. Dissolve the substance of 1 vial in 5 ml of sterile water. Administer 2.5 ml intramuscularly 4 times a day.

Sometimes the dose of drug administered is given in grams per kilogram of patient's wheight. In such cases, the calculation of the amount of the administered drug is the following:

Prescribe a solution of dithylinum (Dithylinum, single dose is 0.002 g/kg) for intravenous administration to a patient whose weight is 70 kg. The drug: ampoules containing 5 ml of 2 % dithylinum solution.

The amount of dithylinum to be administered to the patient: 0.002 (g) · 70 (kg) = 0.14 g. This amount is contained in 7 ml of 2 % dithylinum solution: 0.14 · 100 / 2 = 7 (ml).

Rp.: Sol. Dithylini 2 % – 5 ml
D. t. d. N. 10 in amp.
S. Administer 7 ml intravenously.

Hometasks for Prescription

1. Prescribe 1 000 ml of 2 % chloramine B (*Chloraminum B*) solution. Use for disinfection of instruments.

2. Prescribe 300 ml of 5 % aethacridine lactate (*Aethacridini lactas*) solution. Use for bathing of wounds.

3. Prescribe 0.5 % atropine sulfate (*Atropini sulfa*s) solution. Instill 2 drops into each eye once a day.

4. Prescribe both in full and in short form atropine sulfate (*Atropini sulfas*, the single dose is 0.0005 g) for oral intake 3 times a day.

5. Prescribe analgin (*Analginum*, the single dose is 0.5 g) with dimedrol (*Dimedrolum*, the single dose is 0.01 g) in solution for oral intake 3 times a day.

6. Prescribe platyphyllin hydrotartrate (*Platyphyllini hydrotartras*, the single dose is 0.002 g) in solution for oral intake 3 times a day.

7. Prescribe atropine sulfate (*Atropini sulfas*, the single dose is 0.00025 g) for subcutaneous administration once a day. Drug product: ampoules containing 1 ml of 0.1 % solution.

8. Prescribe platyphyllin hydrotartrate (*Platyphyllini hydrotartras*, the single dose is 0.004 g) for subcutaneous administration 2 times a day. The drug product: ampoules containing 1 ml of 0.2 % solution.

9. Prescribe hygronium (*Hygronium*, the single dose is 0.04 g) for intravenous administration drop-by-drop. The drug product: ampoules containing 0.1 g of dry substance. Before administration, medicinal remedy of one ampoule is dissolved in 100 ml of sterile isotonic sodium chloride solution.

10. Prescribe adrenaline hydrochloride (*Adrenalini hydrochloridum*, the single dose is 0.0003 g) for subcutaneous administration. The drug product: ampoules containing 1 ml of 0.1 % solution.

11. Prescribe tropafen (*Tropaphenum*, the single dose is 0.02 g) for intramuscular administration once a day. The drug product: ampoules containing 0.02 g of dry medicinal remedy.

12. Prescribe cyanocobalamin (*Cyanocobalaminum*, the single dose is 0.0005 g) for intramuscular administration once in 2 days. The drug product: ampoules containing 1 ml of 0.05 % solution.

13. Prescribe streptokinase (*Streptokinasum*, the single dose is 250 000 IU) for intravenous administration drop-by-drop once a day. The drug product: ampoules containing 500 000 IU of dry medicinal remedy. Before administration, medicinal remedy is dissolved according to the ratio 250 000 IU : 50 ml of sterile isotonic sodium chloride solution.

14. Prescribe aminocapronic acid (*Acidum aminocapronicum*, the single dose is 5.0 g) for intravenous administration drop-by-drop once a day. The drug product: vials containing 100 ml of 5 % solution.

15. Prescribe retabolil (*Retabolilum*, the single dose is 0.025 g) for intramuscular administration 1 time in 3 weeks. The drug product: ampoules containing 1 ml of 5 % oil solution.

16. Prescribe tubocurarine chlodire (*Tubocurarini chloridum*, the single dose is 0.0005 g/kg) for intravenous administration. Drug product: ampoules containing 1 ml of 1.5 % solution.

17. Prescribe propanidid (*Propanididum*, the single dose is 0.008 g/kg) for intravenous administration. The drug: ampoules containing 10 ml of 5 % solution.

Suspensions – *Suspensiones* (*Susp.*)
(Nominative case, singular – *Suspensio*; Genitive case, singular – *Suspensionis*)

Suspension is a liquid medicinal form, in which the firm and very small insoluble medicinal substances are in the weighed condition in the liquid (water, vegetable oil, glycerin, etc.).

Suspensions may be used for external application, for oral intake, and for subcutaneous or intramuscular administration. Also, suspensions are administered into body cavities. Suspensions are prescribed both in short and in full form. Short form is used when suspension is prepared on the base of water. The structure of suspension prescription is like solution prescription. Only the word

"*Suspensionis*" ("*Susp.*") is written instead of the word "*Solutionis*" ("*Sol.*"). In the signature, a doctor should indicate "*Shake up before the use*" after the instruction about mode of the suspension use.

Prescribe 10 ml of water suspension containing 0.5 % of hydrocortisone acetate (Hydrocortisoni acetas). Instill 2 drops into each eye 4 times a day. Shake up before the use.

Rp.: Susp. Hydrocortisoni acetatis 0.5 % – 10 ml
D. S. Eye drops. To instill 2 drops into both eyes 4 times a day. Shake up before the use.

Prescribe the Hydrocortisone acetate (Hydrocortisoni acetas) suspension for injections into the joint cavity (the single dose is 0.05 g) once every three days. The drug product: vials containing 5 ml of 2.5 % suspension.

Rp.: Susp. Hydrocortisoni acetatis 2.5 % – 5 ml
D. t. d. N. 2
S. Administer 2 ml into the joint cavity once every 3 days. Shake up before using.

Tinctures and Liquid Extracts – *Tincturae et extracta* (*Tinct., Extr.*)

(Tincture – Nominative case, singular – *Tinctura*;
Genitive case, singular – *Tincturae*;
Extract – Nominative case, singular – *Extractum*;
Genitive case, singular – *Extracti*)

Tinctures and liquid extracts are named "Galenic" drugs after the doctor Galen who suggested their preparation. These medicinal forms are alcoholic (less often alcohol-water or alcohol-ether) extractions from medicinal plant raw material. Tinctures and liquid extracts are prepared without heating. Both tinctures and liquid extracts are dosed in drops. They are stable medicinal forms which can be stored for a long time at room temperature. When preparing tincture, 5 or 10 volumetric parts of the tincture are derived from 1 part of plant raw

material. When preparing liquid extract, 1 or 2 volumetric parts of the extract are derived from 1 part of raw material.

Tinctures and extracts are officinal medicinal forms. Therefore, they are prescribed only in the short form. A doctor designates in the prescription the following information: the medicinal form, the plant name, and total volume of the drug in milliliters (5–30 ml).

Prescribe 20 ml of valerian (Valeriana) tincture. Use 20 drops orally 4 times a day.

Rp.: Tinct. Valerianae 20 ml

D. S. 20 drops orally 4 times a day.

Similar structure of prescription is used for liquid extracts.

Prescribe the liquid extract of motherwort (Leonurum). The single dose is 25 drops. Take orally 3 times a day.

Rp.: Extr. Leonuri fluidi 20 ml

D. S. 25 drops orally 3 times a day.

Except liquid extracts, the pharmaceutical industry manufactures dense extracts (*extracta spissa*) and dry extracts (*extracta sicca*). Therefore, it is necessary to designate in a prescription the information which extract (*liquid, dense* or *dry*) is prescribed. Dense and dry extracts are prepared in capsules, powders, tablets, suppositories, and pills.

Infusions and Broths

(Infusion – Nominative case, singular – *Infusum*;
Genitive case, singular – *Infusi*
Broth – Nominative case, singular – *Decoctum*;
Genitive case, singular – *Decocti*)

The infusions and broths are the water extraction from plant raw materials which is obtained by heating. The infusions are prepared from soft parts of plants (leaves, flowers, and stalks) or from the raw material containing volatile or unstable substances. For preparation, infusions are heated in a boiling water bath for 15 minutes. The broths are obtained from the dense parts of plants – roots, rhizomes, tubers, bark, etc. Broths are heated in a boiling water bath for 30 minutes. After heating, infusions are cooled at room temperature at least for

45 minutes, and broths – for 10 minutes. Then infusions and broths are filtered. If it is necessary, water is added to infusion or broth to the required volume.

The infusions and broths are used both for internal and for external use. For oral intake, infusions and broths are dosed by tablespoons (for adults), dessert spoons or teaspoons.

Infusions and broths are prescribed only in the short form of prescription. They are unstable medicinal forms and should be stored no more than 4 days. They are prescribed for 10–16 intakes. The following information should be designated in the prescription: the name of the medicinal form ("*Infusi*" or "*Decocti*"), the used part of a plant, the plant's name, its weight in grams, and the total volume of infusion or broth.

Prescribe the infusion with digitalis leaves (fol. Digitalis, single dose is 0.05 g). Take orally 3 times a day.

Rp.: Inf. fol. Digitalis 0.5 – 150 ml
D. S. 1 tablespoon orally 3 times a day.

In this case, the quantity of intakes is 10 (it is determined by the doctor). Therefore, the total weight of leaves is 0.05 g · 10 = 0.5 g, and the total volume of infusion is 15 ml · 10 = 150 ml (15 ml is the volume of 1 tablespoon).

The broths are prescribed similarly.

Prescribe the broth with the ipecacuanha roots (rad. Ipecacuanha, single dose is 0.03 g). Take orally 5 times a day.

Rp.: Dec. rad. Ipecacuanhae 0.3 – 150 ml
D. S. Take orally 1 tablespoon 5 times a day.

Mixtures

Mixtures are liquid medicinal forms. The mixtures are prepared by mixing or diluting some firm medicinal remedies in various liquids (water, alcohol, glycerin, vegetable oil), or by mixing liquids (solutions, infusions, broths, tinctures, liquid extracts). Mixtures contain 3 or more ingredients. This medicinal form is used mainly for

oral intake and dosed by spoon (for adults – tablespoon). Mixtures are non-stable medicinal forms and prescribed for 10–12 intakes, that is, for 3–4 days. Mixtures are prescribed only in the full form. In prescription, doctor enumerates all ingredients contained in this mixture. After the name of each component, doctor indicates its amount. The next line is "*M. D. S.*" in which the information for patient about the mode of mixture use is contained.

Prescribe the mixture containing sodium bromide (Natrii bromidum, single dose is 0.5 g) and caffeine benzoate (Coffeini-natrii benzoas, single dose is 0.05 g). Take orally 3 times a day.

Rp.: Natrii bromidi 5.0
Coffeini-natrii benzoatis 0.5
Aquae destillatae ad 150 ml
M. D. S. Take orally 1 tablespoon 3 times a day.

In this example the calculation is fulfilled for 10 intakes. The single dose of sodium bromide is 0.5 g, hence for 10 intakes it is necessary to take 0.5 (g) · 10 (quantity of intakes) = 5.0 (g). The single dose of caffeine benzoate equals 0.05 g, hence for 10 receptions necessary to take 0.05 (g) · 10 (quantity of receptions) = 0.5 (g). For adult patients, mixtures are dosed by tablespoon. One tablespoon contains 15 ml of water. As the total quantity of intakes is 10, it is necessary to take 150 ml of water (15 ml · 10 = 150 ml).

If the mixture contains infusion or broth, it is written in the first line. In such cases, infusion or broth also carries out the function of dissolvent.

Prescribe the mixture containing the infusion of Adonis vernalis grass (herba Adonis vernalis, single dose is 0.5 g), sodium bromide (Natrii bromidum, single dose is 0.5 g), and codeine phosphate (Codeini phosphas, single dose is 0.01 g). Use for oral intake 3 times a day.

Rp.: Inf. herbae Adonidis vernalis 5.0 – 150 ml
Natrii bromidi 5.0
Codeini phosphatis 0.1
M. D. S. Take orally 1 tablespoon 3 times a day.

Prescribe infusion of Adonis vernalis grass (herba Adonis vernalis, single dose is 0.5 g) with may-lily tincture (Convallaria, single dose is 10 drops). Use for oral intake 3 times a day.

Rp.: Inf. herbae Adinidis vernalis 5.0 – 150 ml
Tinct. Convallariae 2 ml
M. D. S. Take 1 tablespoon orally 3 times a day.

The order of calculation of the may-lily tincture volume is the following. It is known, that 50 drops are contained in 1 ml of alcoholic solution. It is the proportion for calculation of milliliter quantity in which the single dose is contained:

50 drops – 1 ml;
10 drops – *x* ml;
$x = 10 \cdot 1 : 50 = 0.2$ ml.

The total quantity of mixture intakes is 10. Therefore, 2 ml of tincture is necessary for 10 intakes:

$0.2 \text{ ml} \cdot 10 = 2.0$ ml.

Liniments
(**Nominative case, singular – *Linimentum*, Genitive case, singular – *Linimenti***)

Liniment (or liquid ointment) is non-dosed medicinal form for external application. Liniment is dense fluid or gelatinous mass which softens at the body temperature. Unlike ordinary ointments, liniments have more liquid consistence. Liniments are rubbed into the skin.

Liquid oils are used as bases for liniments: liquid paraffin (*Oleum Vaselini*), linseed oil (*Oleum Lini*), sunflower-seed oil (*Oleum Helianthi*), olive oil (*Oleum Olivarum*), etc.

Depending on physico-chemical properties, the liniments are divided into two groups.

1. Homogeneous liniments or liniments-solutions. They are molecular solutions or mixtures of two or more mutually soluble ingredients (for example, mixtures of oils with ether, methyl salicylate, chloroform, etc.) or semi-transparent homogeneous gelatinous mixtures (soaps in alcohol). Also, some solid medicinal substances

(menthol, camphor, anaesthesinum, etc.) may be the components of homogeneous liniments.

2. Liniments-suspensions or liniments-emulsions. They are thin colloids of substances unsolvable in a dispersion medium (smallest powders of zinc oxide, starch in water, glycerin, and oils). Certain emulsifiers are added for the preparation of such liniments. Before the use, these liniments should be shaken up.

Liniment is a convenient form for treatment of burns, frostbites, for cosmetic use, etc.

The liniments are prescribed both in full and in short form of prescription in amount of 50–100 ml.

Prescribe in the full form 100 ml of liquid ointment containing 20 % of chloroform (Chloroformium) and 20 % of methyl salicylate (Methylii salicylas). Use for anointment of the joints.

Rp.: Chloroformii
Methylii salicylatis ana 20 ml
Olei Helianthi ad 100 ml
M. f. linimentum
D. S. Use for anointment of the joints. Shake up before the use.

Prescribe in the short form 50 ml of liniment containing aloe (Aloe).

Rp.: Lin. Aloes 50 ml
D. S. Apply on the injured surface of skin 2 times a day.

The concentration of medicinal remedy in liniment is specified in prescription only if this liniment manufactured with different concentrations.

Prescribe 10 ml of liniment containing 1 % of sanguirithrin (Sanguitrinum). Use for applying on the injured parts of skin 2 times a day.

Rp.: Lin. Sanguitrini 1 % – 10 ml
D. S. Apply on the injured parts of skin 2 times a day.

Aerosols – *Aerosola*
Nominative case, singular – *Aerosolum,* Genitive case, singular – *Aerosoli*)

Aerosol is dispersing system with gas, or gas mixture as dispersed system. The dispersed phase consists of solid particles or liquids. In comparison with usual solutions, aerosols have many advantages in the use. Aerosol provides the highest dispersity of matter, simultaneous and uniform coating of skin or mucosa by medicinal remedies. This medicinal form protects medicinal remedies from aggressive influence of air and light and provides the stable sterility for repeated use. Aerosols are used externally for topical application or for inhalations.

Pharmaceutical industry manufactures different drugs in aerosols. This medicinal form is prescribed only in a short form of the prescription.

Prescribe aerosol "Ingaliptum". Use for inhalation 3 times a day.

Rp.: Aerosoli "Ingalyptum" 30,0
D. S. 1 inhalation 3 times a day.

Hometasks for Prescription

1. Prescribe infusion of Thermopsis grass (*Thermopsis*, single dose is 0.05 g) for oral intake 3 times a day.
2. Prescribe infusion of the roots with rhizomes of Valeriana (*Valeriana*, single dose is 0.5 g) for oral intake 3 times a day.
3. Prescribe wormwood tincture (*Absinthium*, single dose is 10 drops). Use for oral intake 3 times a day before meal.
4. Prescribe Buckthorn liquid extract (*Frangula,* single dose is 30 drops) for oral intake in the evening.
5. Prescribe infusion of Adonis vernalis grass (*Adonis vernalis*, single dose is 0.3 g) with tincture of Lily of the valley (*Convallaria*, single dose is 20 drops) and sodium bromide (*Natrii bromidum*, single dose is 0.3 g). Take orally 3 times a day.

6. Prescribe infusion of Digitalis leaves (*Digitalis*, single dose is 0.1 g) with Strophantus tincture (*Strophantus*, single dose is 5 drops) for oral intake 3 times a day.

7. Prescribe 0.25 % hydrocortisone acetate suspension (*Hydrocortisini acetas*, single dose is 0.025 g). The drug product: vials containing 5 ml of suspension. Administer into the joint cavity once a week.

8. Prescribe zinc-insulin suspension (*Zinc-insulinum*, single dose is 20 IU) in vials containing 5 ml of the drug (in 1 ml – 40 IU of insulin). Administer subcutaneously once a day.

9. Prescribe mixture containing pepsin (*Pepsinum*, single dose is 0.2 g) and hydrochloric acid (*Acidum hydrochloricum dilutum*, single dose is 10 drops). Take orally during a meal.

10. Prescribe infusion of Ipecacuanha roots (*Ipecacuanha*, single dose is 0.05 g) with sodium hydrocarbonate (*Natrii hydrocarbonas*, single dose is 0.5 g). Take orally 4 times a day.

11. Prescribe 10 ml of salbutamol aerosol (*Salbutamolum*). Use for inhalation 3 times a day.

GENERAL PHARMACOLOGY

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

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

Pharmacodynamics is a branch of pharmacology that studies the effects of drugs on the human body (biological effects, localization of drug action and mechanism of action).

Drug Pharmacokinetics

Penetration of Drugs through Biological Membranes

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

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

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

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

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

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

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

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

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

transported inside the cell. For instance, some proteins and peptide hormones are transported into the cells by means of pinocytosis.

Routes of Drug Administration

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

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

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

Since the drug action is developed only when it is entering bloodstream, the term “bioavailability” was proposed. The bioavailability is the part of administered drug dose which reaches the systemic circulation in unchanged form. Bioavailability is given in the percentage of the administered dose. In intravenous administration, medication bioavailability is 100 %.

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

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

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

Intravenous route provides the fast effect and fast appearance of high drug concentration in the heart and CNS (although subsequently the drug redistribution takes place). As a rule, drugs are administered intravenously slowly. The bolus administration, drop-by-drop administration, and infusion are possible. Non-soluble substances, oil solutions, drugs with marked irritating activity, and drugs provoking blood clotting or hemolysis are not administered intravenously.

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

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

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

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

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

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

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

Subcutaneous route is widely used for administration of different drugs, insulin, and vaccines. Subcutaneous injections are painful. The speed of subcutaneous drug absorption is lower than in case of intramuscular administration. If intravenous drug administration is impossible

(e. g., in patients with extensive burns), subcutaneous administration is used for elimination of dehydration, disturbances of electrolyte balance or acid-base balance, and for parenteral feeding. About 1.5–2 *l* of fluids may be administered subcutaneously for 24 hours. The solutions must be isotonic.

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

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

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

Intranasal route is used mainly for treatment of rhinitis. Medicinal forms for intranasal administration include the nasal drops, ointments,

and emulsions. It is necessary to notice that nasal mucosa is characterized by significant blood flow and provides the high degree of drug absorption.

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

Drug Distribution in Organism

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

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

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

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

After absorption, a significant amount of the drug binds with plasma proteins, mainly – with albumins. The high degree of binding is typical for sulfonamides of prolonged action, for semisynthetic penicillins and for some other antibiotics and anti-inflammatory agents, etc. The drugs associated with proteins do not penetrate the

tissues, are poorly filtered in kidneys, accumulated in the body, and lack pharmacological activity. There is dynamic equilibrium between free drug fraction and associated part of drug. As free fraction penetrates the tissues, its amount in plasma is maintained due to the drug releasing from the associated fraction.

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

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

Drug Biotransformation

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

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

There are two main types of drug biotransformation:

– metabolic transformation;

– and conjugation.

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

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

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

Hydrolysis is the way for inactivation of ethers and amides. Due to hydrolysis, the ether or amide bond is destroyed. This reaction takes place in the presence of water. Enzymes which catalyze hydrolysis (esterases) are characterized by substrate specificity. Sometimes, the hydrolysis of initially inactive form of drug results in formation of a metabolite with certain pharmacological activity. That is, the part of modern angiotensin-converting-enzyme inhibitors is prodrugs which are transformed into pharmacologically active agents due to hydrolysis (enalapril is transformed into enalaprilate, fosinopril – into fosinoprilate, etc.).

Conjugation is a reaction of accession of hydrophilic endogenous metabolite to the drug molecule. Previously, endogenous metabolite is activated by formation of macroergic bond at the expense of ATP. Typical reactions of conjugation are the drug binding to the residues of acetic or glucuronic acids, glutathione, sulfates, methyl residue, etc.

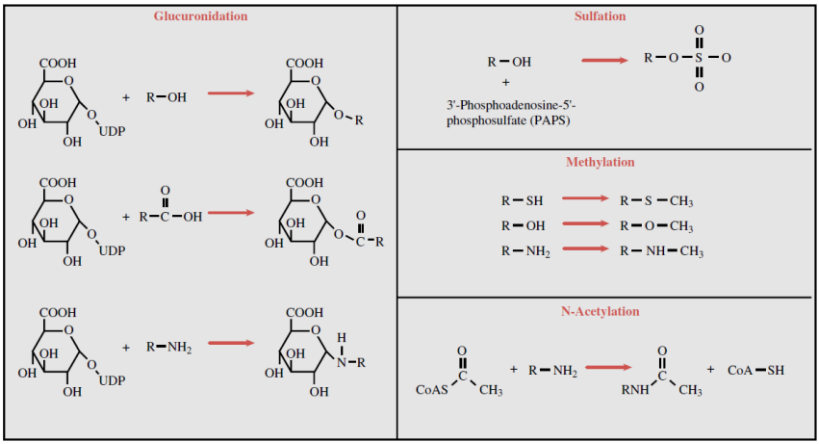

Figure 1 - Examples of phase II conjugation reactions in drug metabolism (by Craig C., Stitzel R.E., 2003)

Conjugation can be the only way of drug biotransformation or can occur after previous metabolic transformation. As a rule, drugs lose the biological activity due to metabolic transformation and conjugation. The drug inactivation is significantly slowed down in patients with hepatic pathology (acute or chronic hepatitis, cirrhosis, etc.). It results in prolongation of drug action and overdose.

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

Drug Excretion

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

The kidneys play a major role in the drug excretion. The drug excretion depends on the processes of filtration, reabsorption, and

secretion. Such substances as water, glucose, amino acids, proteins with molecular weight up to 60 000, and some other substances are filtered in the glomerulus of the kidney nephron. Drug molecules that bind to plasma proteins are not filtered. The filtration speed depends on intensity of renal blood flow. In pathological states with reduced renal blood flow (shock, glomerulonephritis, etc.), filtration is significantly reduced.

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

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

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

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

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

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

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

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

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

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

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

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

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

Drug Pharmacodynamics

Types of Drug Action

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

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

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

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

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

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

Depending on the strength of the bond between the drug and receptor, there are reversible and irreversible actions. In case of reversible action, the function of the target organ (tissue, enzyme, etc.)

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

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

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

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

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

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

Principles of Drug Dosing

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

The minimal drug quantity which causes the development of the minimal therapeutic effect, is called a minimal therapeutic dose.

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

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

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

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

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

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

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

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

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

Phenomena Occurring due to Repeated Drug Administration

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

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

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

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

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

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

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

should be slow, with gradual reduction of the dose and frequency of drug administration.

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

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

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

Physical drug dependence develops due to metabolic restructuring in the organism under the influence of certain drug. That is to say, such drug became essential for function of some organs and systems. The physical dependence is more severe substance dependence. It develops

due to the use of opioid analgesics (morphine, promedolum, heroin, etc.), hypnotic drugs, and some other drug groups.

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

Combined Drug Use

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

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

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

Pharmacokinetic interaction develops during the use of two or more drugs. Drugs can influence one another at the stages of absorption, biotransformation, transport, deposition, and excretion from the body.

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

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

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

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

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

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

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

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

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

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

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

Main Types of Pharmacological Therapy

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

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

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

Preventive therapy is also important because it is used to prevent certain disease. Thus, antiviral drugs are used with the purpose of

preventing epidemics, antiplatelets are used after myocardial infarction with the purpose to prevent platelets aggregation, etc. Preventive therapy is the therapy of future.

Factors Influencing Drug Effects

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

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

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

State Pharmacopoeia contains the highest simple and daily doses of poisoning and powerful drugs that are prescribed to children of different age. Dose calculation for drugs which are absent in Pharmacopoeia is fulfilled according to the following rule: 1/20 part of the adult's dosage is taken for each year of the child's age. It is necessary to notice that such calculations are very approximate

because some children, in their weight and stature, may lag in development at 1–2 years of age.

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

Patient status. Different diseases significantly influence the sensitivity to drugs and their efficacy. Renal and hepatic diseases can cause the retardation of active drug elimination from the organism that increases the complication risks. For their prevention, it is necessary to know the main ways of drug inactivation. Thus, in patients with renal insufficiency, the use of drugs which are inactivated in liver is preferable; in patients with hepatic diseases, preference is given to drugs which are excreted mainly in unchanged form through the kidneys. A frequency of drug complications and intoxications is higher in dehydrated, exhausted and hyposthenic patients. Sometimes, the sensitivity to drugs is changed owing to certain pathology. Thus, hyperthyreosis is accompanied by the increased sensitivity of myocardium to catecholamines. Also, human organism sensitivity to drugs changes during pregnancy, menopause, etc.

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

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

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

studies the influence of daily rhythms on the organism. Chronopharmacology is divided into chronopharmacokinetics and chronopharmacodynamics.

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

Main and Side Drug Effects

The drug action which provides the development of necessary pharmacological effect (blood pressure reduction, pain relief, fewer reduction, etc.) is called main action. However, besides the main effects, all drugs exhibit side effects which are undesirable for the organism. Side effects develop in the range of therapeutic drug doses. Thus, a hypnotic agent chloral hydrate significantly irritates the mucous membranes when used in therapeutic doses. Side effects may be primary and secondary. Primary side effects arise as a direct result of the drug influence on a certain substrate. That is, nausea and vomiting induced by ether inhalation develop due to irritative action of ether on gastric mucosa. Secondary side effects develop indirectly. Thus, severe destructive pneumonia can develop due to aspiration of vomit into the respiratory tract during ether narcosis.

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

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

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

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

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

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

Fetotoxic effect is the result of undesirable effects of the drug on the fetus during the later stages of pregnancy. Herewith, a quality of fetus reaction is virtually identical to the reaction of an adult and can cause the development of severe pathology or death of either a fetus or a newborn.

It is necessary to notice that drugs can influence the fetus even on the step of progenesis by affecting the reproduction and trophism of male and female sex cells and by causing the chromosomal aberrations or gene mutations. Such drug ability to cause the stable damages of cells and their genetic apparatus which is accompanied by genotype change

in the child is called mutagenic action. Thereby, it is necessary to stop taking any drugs at least 6 months before the planned pregnancy.

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

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

General Principles of Treatment of Acute Poisoning

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

Maximum cases of poisonings (accidental poisoning) occur in children aged from 1 to 4 years. Among adults, there are both accidental and deliberate (suicidal) poisonings. Moreover, suicidal poisonings are common among young people aged from 16 to 20 years and among elderly. The poisonings caused by alcohol, medicines (hypnotic drugs, antihypertensive drugs, etc.), and household chemicals (insecticides, dyes, gasoline, kerosene, antifreeze, etc.) are dominant. During summer, the poisonings caused by such plants as belladonna, herb Paris (Crow's eye), jimsonweed, and mushrooms (especially, by *Amanita phalloides*) are common. The incidents of substance dependence are widespread among teenagers inhaling insecticides (Chlorophos [Metrifonate], Carbophos [Malathion], etc.), gasoline, kerosene, etc. It is commonly accompanied by severe poisonings with fatalities. It is necessary to notice that poisons containing toluene cause the condition which is like action of hallucinogen LSD (lysergic acid diethylamide). Such substances can cause psychical dependence with fast personality degradation.

There are acute and chronic poisonings. The chronic poisonings develop due to repeated intake of small doses of toxic substances and

are characterized by slow progressive development of symptoms. Most of professional diseases caused by toxic substances are chronic poisonings.

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

A treatment of acute poisonings includes the following measures:

– poison elimination from the body;

– poison inactivation;

– symptomatic therapy (maintenance of organism functions).

Elimination of Poison from the Body

Elimination of Unabsorbed Poison

After the skin contact with poison drops, it is necessary to rinse it from the skin with warm water and soap. There are specific antidotes which neutralize the poison or interfere with its influence upon the skin. If poison gets on the conjunctiva or cornea of the eye, it is necessary to rinse them with warm normal saline, milk, or water during 10–15 minutes. After this, 0.5–1 % dicain (tetracaine hydrochloride) solution is applied into the conjunctival sack. If phosphorus organic compounds get in the eyes, they should be rinsed with 3 % sodium hydrocarbonate solution.

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

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

Gastric lavage or induced vomiting is used for the poison elimination from the stomach. 5–10 % sodium chloride solution is used (2–4 teaspoon of sodium chloride dissolved in a glass of water) for inducing vomiting. This solution irritates the gastric mucosa

accompanied by spasm of pyloric sphincter and the movement delay of poison into intestine. It results in the reduction of poison absorption. Ipecacuanha syrup may be prescribed for children. This syrup induces the vomiting in 5–20 minutes after intake. Also, apomorphine may be administered subcutaneously or intramuscularly to adults or children over 5 years of age. Simultaneously, ephedrine is administered intramuscularly to prevent hypotension.

Inducing vomiting is contraindicated in the following cases:

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

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

In other cases, gastric lavage should be fulfilled even after vomiting. Gastric lavage is fulfilled several times with interval 3–4 hours until complete purification of stomach from poison. To prevent body hypothermia, the warm water or solutions are used for gastric lavage. The use of normal saline, Rheopolyglucin, or potassium permanganate for gastric lavage is preferable. If necessary, active carbon or other adsorbents may be added to the mentioned solutions. Also, milk or egg protein solution (12 egg whites in 1 litre of boiled water) may be used. But the use of milk is contraindicated in poisonings caused by lipid-soluble substances, because butterfat facilitates the poison absorption, relaxes pyloric sphincter, and promotes the poison transition into the intestine.

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

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

Siphonic enemas are also used to remove poisons from the intestines. For a siphonic enema 8–10 liters of water are used.

Elimination of Poison from Blood

Before elimination of poison from the blood, it is necessary to provide a patient with fresh air and administration of analeptics (caffeine, aethymizole), or carbogen inspiration. In poisonings caused by irritative substances for prevention of pulmonary edema, a patient should avoid doing sharp movements. Such patients should be warmed and receive inhaled oxygen. For moistening, oxygen is passed through the water in Bobrov's apparatus. The anti-foaming agents (ethyl alcohol or antifomsilanum) are administered to the patient when the symptoms of pulmonary edema develop. After that, measures to eliminate poison from the blood are carried out: forced diuresis, hemodialysis, hemosorption, blood replacement, etc.

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

The technique of forced diuresis depends on poisoning severity. In mild poisoning, a patient receives a large volume of drinking water and furosemide perorally. The patient should drink the necessary water volume during 8–12 hours. The volume of drinking water should be at least of daily water demand. In case of average poisoning, drugs which can bind poisoning are administered intravenously (Neohemodesum, Polyglucinum, Reopolyglucinum, etc.). In case of acid poisoning (barbiturates, acetic acid, salicylic acid derivatives, etc.), 2–4 % solution of sodium hydrocarbonate is also administered intravenously. After that, 10 % glucose solution with potassium chloride is

administered intravenously. In severe cases of poisoning, Neohemodesum, Reopolyglucinum, and sodium hydrocarbonate solution are administered for 1 hour. After this, osmotic diuretics (mannitol) or loop diuretics (furosemide) are administered. A volume of fluids administered intravenously should be equal to the volume of excreted urine. In case of super-severe (terminal) poisoning, initially, it is necessary to restore the breathing and the blood circulation. After that, forced diuresis is carried out.

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

Blood substitution is effective when a volume of transfused blood is 1.5–2 times more than a volume of patient's blood. To prevent hypocalcemia, 10 ml of 10 % calcium chloride solution is added to each 500 ml of citrated blood. Blood substitution is effective if it is carried out during the first hours of poisoning. As a rule, this measure is ineffective if carried out 8–29 hours after poisoning.

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

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

Hemoperfusion is a method of filtering the blood when the blood passes through a column with absorbtive properties aiming at removing specific toxic substances from the blood. The adsorbent substances most commonly used in hemoperfusion are resins and

activated carbon. Hemoperfusion is an extracorporal form of treatment because the blood is pumped through a device outside the patient's body. By means of hemoperfusion, not only the poisons that do not bind to plasma proteins, but also other poisons may be eliminated from the body.

Inactivation of Toxic Substance

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

– antidotes which bind poison and prevent the absorption of poison by their presence;

– antidotes which accelerate the poison biotransformation;

– antidotes which are pharmacological antagonists.

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

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

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

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

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

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

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

Antidotes Accelerating Biotransformation of Poison

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

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

Antidotes – Pharmacological Antagonists

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

Symptomatic Therapy of Acute Poisonings

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

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

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

An elimination of hypoxia and pulmonary edema is the primary task in patients with acute heart failure. Thereto, the fluid pumping from the lungs is fulfilled. Also, antifoam agents are administered (ethyl alcohol or antifomsilan). In Bobrov's apparatus, oxygen is passed through the water with ethanol added (10 ml of 30–40 %

ethanol). Antifomsilan is used as aerosol or administered (5–8 drops) into the respiratory ways. In the case of progressive hypoxia, the artificial respiration is used. Ganglion blocking drugs are used for decreasing preload and afterload of the heart. Simultaneously, furosemide is administered. It increases diuresis and reduces the circulating blood volume that results in decreasing preload. It is necessary to notice that osmotic diuretics are contraindicated in such cases. Also, cardiac glycosides are administered to a patient. Albumin is used for restriction of fluid transudation into the alveoli. Prednisolone, calcium gluconate, and antagonists of H_1-histamine receptors (e. g., dimedrolum) are used to reduce vascular permeability.

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

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

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

Hyperthermia can develop due to hypoxia or poison influence upon the thermoregulatory centre. Organism cooling may be carried out by means of the cold which is applied upon the head and regions of large vessels. Also, antipyretic drugs are administered intramuscularly or intravenously together with dibazol or benzohexonium (for the increase of heat emission). In severe cases, dimedrolum or diprazine are administered.

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

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

Step 1. Tasks for Self-Control
General Pharmacology

1. Drug *A* has been prescribed to a patient. In several days, the action of the drug has significantly decreased, and the increased dose of the drug is necessary for achievement of initial effect. What is the name of this phenomenon?

A. Idiosyncrasy.
B. Tachyphylaxis.
C. Tolerance.
D. Drug dependence (drug addiction).

E. Cumulation.

2. Drug *A*, which decreases the blood clotting, has been prescribed to a patient with thrombosis of veins. After several days the signs of overdose have developed in patient. The level of drug *A* in blood significantly exceeded the top border of therapeutic concentration. What is the name of this phenomenon?

A. Antagonism.

B. Cumulation.

C. Tachyphylaxis.

D. Tolerance.

E. Potentiation.

3. Substance *A* increases the tone of smooth muscles of intestine. This effect is not observed in presence of substance *B*. But the tone of intestine is increased if concentration of substance *A* is enhanced 10 times and concentration of substance *B* is not changed. What is this type of drugs interaction called?

A. Non-equilibrium antagonism.

B. Indirect antagonism.

C. Equilibrium antagonism.

D. Potentiation.

E. Synergism.

4. The biological activity of xenobiotics in human organism is decreased due to reactions of:

A. Hydration.

B. Amination.

C. Carboxylation.

D. Dehydration.

E. Hydroxylation.

5. The synthesis of ATP in cells is blockaded in pharmacological experiment. What type of drugs transport through the bio membranes will undergo the greatest changes?

A. Filtration.

B. Passive diffusion.

C. Osmosis.

D. Active transport.

E. Simplified diffusion.

6. A man, 36-year-old, with craniocerebral trauma has diminished breath sounds, thready pulse, reflexes are absent. What route of administration of pyracetam is the most appropriate in this case?

A. Inhalation.

B. Subcutaneous.

C. Intravenous.

D. Peroral.

E. Rectal.

7. A man abused drug *A* during a long time. After the interruption of this drug use, the abstinence has developed in this patient. But the signs of abstinence are eliminated after the use of drug *B*. This phenomenon is an example of:

A. Psychic dependence.

B. Potentiation.

C. Tolerance.

D. Physical dependence.

E. Cross-dependence.

8. For the passive diffusion of medicinal substance through the biological membranes the following is typical:

A. Moving of molecules according to the concentration gradient.

B. Possibility of competition of two substances for one transport mechanism.

C. Presence of protein carrier in membranes.

D. Presence of external source of energy.

E. Moving of molecules through membranes by means of their kinetic energy.

9. What property of medicinal substances promotes their cumulation?

A. High degree of dissociation.

B. High degree of biotransformation.

C. High solubility in lipids.

D. Low degree of binding with proteins.

E. High degree of binding with proteins.

10. Amebiasis was diagnosed in a patient, who had appealed to the doctor. Doctor prescribed tetracycline to this patient. What type of action was used in this case?

A. Irreversible action.

B. Direct action.

C. Etiotropic action.

D. Reflex action.

E. Main action.

11. It is necessary to introduce the drug into an organism in a definite period for creation of effective concentration of the drug in the organism. Point out the pharmacological parameter which should be considered at a choice of drugs introduction rhythm.

A. Constant of elimination.

B. Breadth of therapeutic action.

C. Coefficient of diffusion in intestine.

D. Period of half-life.

E. Degree of binding with proteins.

12. The tranquilizer diazepam in average therapeutic doses was prescribed to a patient with disturbing-imaginary state. But due to the genetically determinant enzymopathy the action of the drug was so strong, that the marked hypnotic effect was showed in the patient. What is such atypical reaction to a drug called?

A. Dependence.

B. Idiosyncrasy.

C. Allergy.

D. Tachyphylaxis.

E. Tolerance.

13. What is the name of the psychic and physical disturbances in narcomaniac, which develop due to interruption of narcotic intake?

A. Abstinence.

B. Idiosyncrasy.

C. Tachyphylaxis.

D. Euphoria.

E. Tolerance.

14. The recommended route of drugs administration to a comatose patient is:

A. Rectal.

B. Intravenous.

C. Inhalation.

D. Peroral.

E. Subcutaneous.

15. A woman intakes tranquilizers in the second part of pregnancy. The delivery develops in time, but the child was born with different anomalies of development (labium leporium, polydactyly). What is such drug action called?

A. Carcinogenic action.

B. Mutagenic action.

C. Embryotoxic action.

D. Fetotoxic action.

E. Teratogenic action.

16. Several injections of ephedrine hydrochloride had been given in short period of time to a patient with acute dropping of blood pressure. But the reaction of vessel to the last introduction was much lower, than to previous injections. What is the cause of this phenomenon?

A. Ricochet syndrome.

B. Idiosyncrasy.

C. Tolerance.

D. Cumulation.

E. Tachyphylaxis.

17. The significant psychic, neurologic, and somatic disturbances develop in an addict after the cessation of narcotic action. What is the name of this phenomenon?

A. Tolerance.

B. Physical dependence.

C. Abstinence.

D. Sensitization.

E. Cumulation.

18. A pregnant woman had taken high doses of retinol during the first trimester of pregnancy. This caused hypervitaminosis. The pregnancy developed normally, but the newborn had the anomalies of development. What is such negative drug action called?

A. Carcinogenic.

B. Teratogenic.

C. Embryotoxic.

D. Fetotoxic.

E. Mutagenic.

19. Some drug in tablets was prescribed to a patient with hypertensive disease. What factor does not have the influence upon absorption of the drug from intestine?

A. Activity of microsomal hepatic enzymes.

B. Intake of other drugs.

C. Food intake.

D. Solubility of the drug in water or in lipids.

E. Acidity of stomach juice.

20. Digitoxin was prescribed to a patient with chronic heart failure. After several weeks of treatment, the following symptoms of glycoside intoxication had developed in the patient: bradycardia, nausea, extrasystoles. But the dose did not exceed the average therapeutics and the term of treatment course did not terminate. What is this phenomenon called?

A. Idiosyncrasy.

B. Material cumulation.

C. Functional cumulation.

D. Tolerance.

E. Tachyphylaxis.

21. A doctor has prescribed diclofenac-sodium and prednisolone to a patient with serious polyarthritis. The doctor considers, that in case of simultaneous introduction of non-steroid anti-inflammatory drugs and glucocorticoids their action will significantly increase because the drugs have different mechanisms of action. What is such type of drugs interaction called?

A. Pharmacokynetical interaction.

B. Direct synergism.

C. Physicochemical interaction.

D. Pharmaceutical interaction.

E. Indirect synergism.

22. It is known that the substance has significant hydrophilic properties. What pharmacological peculiarity is typical for this substance?

A. Ability to freely penetrate the blood-brain barrier.

B. High bioavailability.

C. Rapid renal elimination.

D. Biotransformation in liver.

E. Ability to penetrate cells.

23. During an experiment the acetylsalicylic acid was introduced in different parts of gastrointestinal tract. In what part of GI-tract is this drug absorbed with the maximal speed?

A. Stomach.

B. Large intestine.

C. Oral cavity.

D. Duodenum.

E. Small intestine.

24. The following type of reaction should be expected in case of prescribing drugs to a pregnant woman:

A. Mutagenic.

B. Teratogenic.

C. Embryotoxic.

D. Fetotoxic.

E. All from above.

25. Indicate the properties of a drug which depend on the time of drugs' introduction.

A. Speed of drug absorption.

B. Toxicity.

C. Qualitative activity.

D. Quantitative activity.

E. All from above.

26. A doctor has introduced the caffeine intramuscularly to a patient with alcohol intoxication. What is the principle which is the base of expediency for such treatment?

A. Summation.

B. Physiological antagonism.

C. Synergism.

D. Potentiation.

E. Competitive antagonism.

27. The metabolism of drugs in fetus is significantly slower than in adult organism. This feature of fetus pharmacokinetics is due to:

A. Insufficiency of tissue receptors.

B. Significant permeability of blood-tissue interfaces.

C. Significant volume of extracellular fluid.

D. Capacity of skin to absorb and excrete the drugs.

E. Functional insufficiency of enzymes or their absence.

28. The influence of some adverse factors, such as drugs, before pregnancy increases the possibility of birth of the child with genetic abnormalities. What is this action called?

A. Carcinogenic.

B. Embryotoxic.

C. Teratogenic.

D. Mutagenic.

E. Fetotoxic.

29. It is known that in persons with genetically determined insufficiency of glucoso-6-phosphate dehydrogenase of erythrocytes the prescription of some antimalarial drugs can cause the hemolysis of erythrocytes. What is this atypical reaction upon drugs called?

A. Idiosyncrasy.

B. Tolerance.

C. Allergy.

D. Sensitization.

E. Tachyphylaxis.

30. The drug *A* with significant solubility in lipids was prescribed to a patient. What is the main mechanism of its absorption?

A. Interaction with transport proteins.

B. Filtration.

C. Passive diffusion.

D. Active transport.

E. Pinocytosis.

31. During operation the anaesthesiologist used the nitric oxide as general anaesthetic. This drug has significant lipophilic properties. What is the mechanism of this drug penetration through biological membranes?

A. Pinocytosis.

B. Active transport.

C. Simplified diffusion.

D. Filtration.

E. Passive diffusion.

32. Benzylpenicillin sodium is injected to a patient with pneumonia in a dose of 500 000 units of action 6 times daily. After another injection there arose fever, spasms, and then the patient lost consciousness. What has happened to the patient?

A. Medicines tolerance.

B. Idiosyncrasy.

C. Anaphylactic shock.

D. Tachyphylaxis.

E. Cumulation.

33. A victim was delivered to an emergency station by an ambulance with the following diagnosis: displaced fracture of the middle one-third of the hip. With the purpose of bone fragments reposition 10 ml of 2 % dithylinum solution was injected to the patient intravenously. In consequence of that a long-lasting apnea and muscle relaxation developed. What enzyme deficiency causes such side effect?

A. Pseudocholinesterase.

B. N-acetyltransferase.

C. Acetylcholinesterase.

D. Glucose-6-phosphate dehydrogenase.

E. Methemoglobin reductase.

34. A medicine *A* was prescribed to a patient. In a few days the drug effect has considerably decreased and to get the initial effect it was necessary to increase the dose. What is this phenomenon called?

A. Idiosyncrasy.

B. Tachyphylaxis.

C. Drug dependence.

D. Tolerance.

E. Cumulation.

35. During an operative intervention with the use of muscle relaxants breath disorder appeared. Injection of proserinum led to improvement. What is such drug interaction called?

A. Cumulation.

B. Antagonism.

C. Synergism.

D. Incompatibility.

E. Tachyphylaxis.

36. A patient suffering from epilepsy has been continuously receiving 0.2 g dose of phenobarbital daily. Recently, the attacks became more frequent, dysphoria was observed. Which process became the cause of the deterioration of the patient's status?

A. Glycolysis inhibition.

B. Liver monooxygenase system enzymes inhibition.

C. Lipolysis activation.

D. Gluconeogenesis activation.

E. Liver monooxygenase system enzymes induction.

37. In the postoperative period promedol was injected continuously to a patient. Withdrawal of the drug caused serious mental and somatic disturbances. What is this phenomenon called?

A. Output syndrome.

B. Idiosyncrasy.

C. Abstinence syndrome.

D. Tachyphylaxis.

E. Steal syndrome.

38. A man, 36-year-old, with a craniocerebral trauma has diminished breath sounds, thready pulse, reflexes are absent. What route of pyracetam administration is the most appropriate in this case?

A. Inhalation.

B. Subcutaneous.

C. Peroral.

D. Rectal.

E. Intravenous.

39. Ambulance has been called to a 22-year-old man for the reason of bronchial asthma attack. What route of salbutamol introduction is the most appropriate in this case?

A. Sublingual.

B. Inhalation.

C. Intramuscular.

D. Intravenous.

E. Subcutaneous.

40. Angina pectoris attack happened to a man, 48-year-old. A doctor prescribed him a pill of nitroglycerine sublingually. Why has the doctor chosen a sublingual method of medicine administration?

A. Effect develops faster.

B. Only because it damaged the liver.

C. Drug elimination by gastric juice.

D. Low intestinal absorption.

E. It is activated by saliva.

41. Ambulance has been called to a 22-year-old man because of asthmatic status. What route of adrenaline hydrochloride administration is the most appropriate in this case?

A. Sublingual.

B. Inhalation.

C. Intramuscular.

D. Subcutaneous.

E. Intravenous.

42. Intramuscular injection of benzylpenicillin sodium was made to a man, 28-year-old, because of a shoulder phlegmon. After that the man had tachycardia, thready pulse and arterial pressure decreased to 80/60 mm Hg. What kind of pharmacological reaction has developed?

A. Peripheral effect.

B. Anaphylactic shock.

C. Central effect.

D. Reflex effect.

E. Potentiation.

43. Phenobarbital was prescribed to a man, 56-year-old, suffering from insomnia. The sleep rhythm has been normalized. But gradually, for 2 months, the effect of the drug had decreased, and insomnia arose. What reason has caused the reduction of the hypnotic effect?

A. Tachyphylaxis.

B. Low solubility.

C. Bad absorption in the stomach.

D. Tolerance.

E. Accumulation in lipids.

44. During the fetal period metabolism of medications is considerably slower than in adult age. The specified feature of a fetus pharmacokinetics is primarily caused by the following:

A. "Maturation" of receptors in organs at different terms.

B. High permeability of blood-tissue interfaces.

C. Significant volume of extracellular liquid.

D. Ability for absorption and release of water-soluble drugs by skin.

E. Functional imperfection of most enzymes, their absence.

45. It is known that people with insufficiency of glucose-6-phosphate dehydrogenase of red blood cells, caused genetically, may develop hemolysis of these cells as a reaction to some antimalarial medication prescription. What is such atypical reaction to medications called?

A. Tolerance.

B. Idiosyncrasy.

C. Sensitization.

D. Allergy.

E. Tachyphylaxis.

46. How can be explained the fact that for tuberculosis treatment an isoniazid dose is being selected individually with obligatory control of contents of the medication in urine after its first intake?

A. Development of hemolytic anemia.

B. Hyperglycemia after the drug intake.

C. Genetically caused speed of acetylation of the drug.

D. Development of renal insufficiency.

E. Irritative effect of the drug.

47. A patient with hypertension has been taking an antihypertensive medication for a long time, but suddenly he stopped the intake. After that the patient's status worsened, the hypertensive crisis developed. What kind of collateral action has developed?

A. Withdrawal syndrome.

B. Dependence.

C. Cumulation.

D. Tolerance.

E. Sensitization.

48. An out-patient with chronic cardiac insufficiency has been taking digoxin in therapeutic doses during several months. At a certain stage of treatment overdose symptoms appeared. What phenomenon underlies the development of such complication?

A. Tachyphylaxis.

B. Drug habituation.

C. Sensitization.

D. Functional cumulation.

E. Material cumulation.

49. At a stomatologist, a patient developed an attack of bronchospasm which was cured with 5 % ephedrine hydrochloride solution injection. In 20 minutes, the attack repeated. An additional injection of ephedrine had no effect due to tachyphylaxis. What mechanism underlies this phenomenon?

A. Induction of microsomal enzymes of the liver.

B. Exhaustion of noradrenaline depot in presynaptic endings.

C. Inhibition of adrenoreceptors.

D. Activation of adrenoreceptors.

E. Material cumulation of the drug.

50. A patient with atypical reaction developing in the result of drug administration is delivered to intensive care unit. Indicate the name of increased sensitivity and atypical reaction to the drug.

A. Idiosyncrasy.

B. Summation.

C. Tolerance.

D. Dependence.

E. Cumulation.

51. A patient with morphinism is delivered to narcological unit. In the result of examination, a doctor indicated the decrease of morphine action. What is the phenomenon of drug action weakening in the result of repeated drug administration called?

A. Summation.

B. Material cumulation.

C. Functional cumulation.

D. Antagonism.

E. Tolerance (accustoming).

52. What medicinal form provides the fastest and most complete absorption of a drug in gastrointestinal tract?

A. Granules.

B. Tablets.

C. Capsules.

D. Dragee.

E. Solutions for internal use.

DRUGS INFLUENCING PERIPHERAL NERVOUS SYSTEM

Drugs Influencing Afferent Innervation

Drugs influencing afferent innervation are classified as follows:

1. Drugs reducing the sensitivity of nervous endings and interrupting the conductibility of afferent nerves:

– local anaesthetics;
– astringent drugs;
– enveloping agents (demulcents);
– adsorbing drugs.

2. Drugs stimulating the endings of afferent nerves:

– irritative drugs;
– emetic drugs;
– laxative drugs;
– expectorants;
– amarines.

Local Anaesthetics

On the locus of applying, local anaesthetics block the sensitivity of afferent nerve endings and impulse conduction in nervous fibers. It results in the loss of pain sensitivity. High concentrations of local anaesthetics also suppress temperature sensitivity and other kinds of sensitivity. In the last turn, reaction to touch and pressure is suppressed.

The history of local anaesthetics began in 1859, when Niman and Vekler singled out alkaloid cocaine from South American coca plant.

Chemically, local anaesthetics are esters of aromathic acids (benzoic, para-aminobenzoic, etc.) or substituted amides. Molecules of local anaesthetic consist of aromathic nucleus connected by means of ester or amide bond with amino alkyl group. Aromatic nucleus is lipophilic part of molecule that provides drug ability to penetrate through the cell membrane. Intermediate chain, containing ester or amide bond, provides the stability of drug and duration of its effect.

Thus, anaesthetics containing ester bond are hydrolyzed fairly quickly by plasma esterases. Amino acid residue determines the molecule ability to form the salt with acids and consequently the drug ability to dissolve in water.

Local anaesthetics (except benzocaine) are manufactured as salts of hydrochloric acid. Anaesthesia develops only after the salt hydrolysis with base release. Hydrolysis occurs at pH = 7.35–7.4. In acidic environment (in inflammation) hydrosysis does not occur, therefore, local anaesthetics are ineffective.

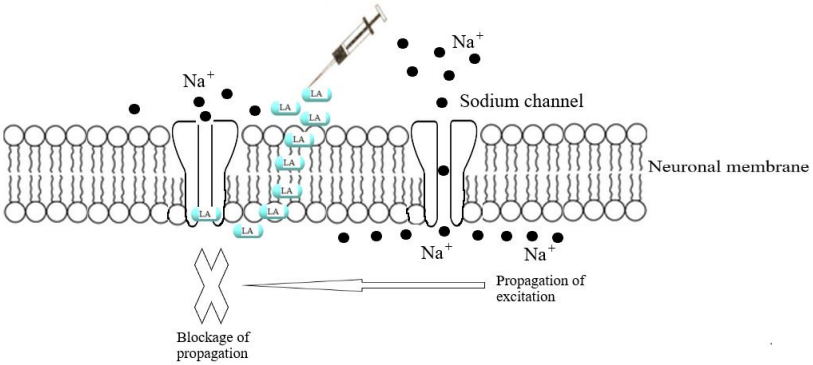

Figure 2 – Mechanism of action of local anaesthetics.
LA – local anaesthetic molecules;
Na^+ - sodium ions.

Mechanism of action of local anaesthetics is associated with the block of potential-dependent sodium channels that inhibit the formation of action potential and its propagation. Lipid-soluble molecules of local anaesthetic penetrate through the membrane of a nervous fiber and block sodium channels from the inside. It is possible, that molecules of local anaesthetic competitively replace calcium ions involved in regulation of membrane permeability for sodium. This causes inhibition of calcium-dependent phospholipases and ATPase with the following reduction of concentration of fatty acids and phospholipid lyso-forms, that results in the change of structure and

function of sodium channels. Local anaesthetics block not only permeability for sodium and calcium, but also potassium permeability.

There are several types of local anaesthesia: terminal (superficial), conduction (regional), infiltration, spinal anaesthesia, etc.

For terminal anaesthesia, preparation of local anaesthetic is applied on mucosa, burn, or wound that provides the loss of pain sensitivity. Superficial anaesthesia is widely used to treat burns and wounds, in ophthalmology, urology, otorhinolaryngology, etc.

Conduction anaesthesia develops due to blockage of a large nervous fiber by local anaesthetic. A loss of pain sensitivity develops in the area which is innervated by this nerve. Regional anaesthesia is frequently used in stomatological, surgical, and therapeutic practice.

Infiltration anaesthesia is a result of injectional saturation of tissues by anaesthetic solution. It is widely used in surgical practice.

For spinal anaesthesia, a local anaesthetic solution is injected into the subarachnoidal space, which causes a block of impulse transmission through the dorsal roots of the spinal cord. Spinal anaesthesia is used in operations of lower extremities and pelvic organs.

Local anaesthetics differ among themselves by efficacy, duration of action, ability to penetrate through mucous membranes, and toxicity. There are drugs of choice for each type of local anaesthesia.

Local anaesthetics are classified as follows:

1. Drugs for superficial anaesthesia: *cocaine, dicaine (tetracaine), anaesthesine (benzocaine), and pyromecaine (bumecaine)*.

2. Drugs which are used mainly for infiltration and conduction anaesthesia: *novocaine (procaine), trimecaine, bupivacaine (marcaine), ultracaine (articaine)*.

3. Drugs which are used for all types of local anaesthesia: *lidocaine (xylocaine)*.

The requirements for local anaesthetics are the following:

– high eficacy and selectivity of action;

– lack of negative influence upon surrounding tissues;

– short latent period;

– duration of action corresponding to a certain operation.

It is also desirable, that a drug constricts vessels or, at least, does not cause vasodilation.

Resorptive effects of local anaesthetics are quite diverse. These effects are marked in case of intravenous administration of local anaesthetic or due to absorption of a large drug amount into systemic bloodstreem. Thus, slow intravenous novocaine administration is accompanied by gradually developing feeling of loss of your own weight, analgesia, CNS depression, novocaine-induced sleep, and narcosis. Most significant inhibition is observed in polysynaptic neuronal pathways of spinal cord, ascending part of reticular formation, and cortex.

Together with central effects, changes in activity of peripheral organs develop. Novocaine inhibits vegetative ganglia that results in antispasmodic effect and lowering of the blood pressure. The drug suppresses impulse transduction through the conductive system of the heart, reduces the heart rate, and exhibits antiarrhythmic action.

The described effects, to a greater or lesser extent, are typical for all local anaesthetics. Bupivacaine has more marked cardiotoxic action.

According to the chemical structure, local anaesthetics are classified as follows:

1. Derivatives of ethers of benzoic acid and amino alcohols: *cocaine*.

2. Derivatives of ethers of para-aminobenzoic acid: *novocaine (procaine), dicaine (tetracaine), and anaesthesine (benzocaine)*.

3. Substituted amides of acetanilide: *lidocaine, trimecaine, pyromecaine (bumecaine), bupivacaine (marcaine), and ultracaine (articaine).*

Comparative characteristics of local anaesthetic drugs are given in the table 4.

Table 4 – Comparative characteristics of local anaesthetics

Drug	Activity			Toxicity
	terminal anaesthesia	infiltration anaesthesia	conduction anaesthesia	
Novocaine	0.1*	1	1	1
Dicaine	10	–	–	20
Trimecaine	0.4	2–3	2.5–3.5	1.3–1.4
Lidocaine	0.6	3–4	2.5–3.5	1.5–2
Ultracaine	0.5	3–5	3–5	1
* high concentration (more than 10–20 %) of novocaine causes corneal anaesthesia, but damages epithelium				

Derivatives of Ethers of Benzoic Acid and Amino Alcohols

Cocaine was first anaesthetic used in medicine. Presently, its use is stopped due to high toxicity and ability to cause drug dependence. Most commonly, cocaine was used in ophthalmology. Besides the marked anaesthetic effect (which lasts up to 1 hour), cocaine constricts vessels of the sclera and dilates the pupil. Intraocular pressure is reduced. These effects develop due to indirect adrenomimetic action of cocaine. Long-term use of cocaine leads to epithelial cleavage of cornea and its ulceration. In resorptive action, cocaine stimulates central nervous system. The following symptoms develop: loss of feeling of hunger and tiredness, psychomotor excitement, and euphoria. Cocaine stimulates respiratory, vasomotor, and emetic centres of medulla oblongata. Cocaine can provoke convulsions. Also, cocaine causes tachycardia and hypertension. If cocaine dose is very high, stimulation of central nervous system is replesed by its inhibition. Death occurs due to depression of vital centres of medulla oblongata (primarily, respiratory centre). In cocaine overdose, diazepam or barbituric acid derivatives (thiopental sodium, hexenal) are administered for reduction of excessive excitation of CNS and

adrenergic antagonists – for normalization of heart rate and blood pressure. Artificial respiration is used in patients with respiratory depression.

Chronic cocaine intake leads to drug dependence – cocainism. Psychical, but no physical, dependence develops in cocaine-dependent patients. In this case, sudden cessation of cocaine intake results in severe psychical state including dysphoria, depression, drowsiness, fatigue, and increased craving for cocaine. Tolerance to cocaine manifestes insignificantly or does not develop.

Derivatives of Ethers of Para-Aminobenzoic Acid

Dicaine (tetracaine) is local anaesthetic used only for topical anaesthesia. The drug is 10 times more potent anaesthetic than cocaine, but its toxicity is 2–5 times more. Dicaine does not cause mydriasis and does not influence intraocular pressure. Dicaine dilates vessels therefore its combination with adrenaline is expedient. At terminal anaesthesia, the drug is easily absorbed through mucous membranes and can cause toxic effects and patient's death due to overdose. Therefore, dosage of dicaine should be strictly observed.

Anaesthesine (benzocaine) is poorly soluble in water; therefore, it is used in the following medicinal forms: powders for external application, ointments, pastes (anaesthesia of wounds or skin ulcers, itchy skin, etc.), rectal suppositories (hemorrhoids and perianal fissures), and tablets or powders for oral intake (stomach pain and kinetosis).

Novocaine (procaine) is used for infiltration and conduction anaesthesia. Duration of infiltration anaesthesia induced by novocaine is 0.5–1 hour. The drug is low toxic. Novocaine is hydrolyzed mainly by butyrylcholinesterase and excreted by kidneys in conjugated form with glycine or glucuronic acid. Novocaine is seldom used for terminal anaesthesia because poorly penetrates through mucous membranes. The drug does not influence vascular tone or insignificantly relaxes vessels. Therefore, it is used with the added adrenaline solution. In this case, duration of novocaine-induced anaesthesia increases to 1.5–2 hours. The main metabolites of novocaine are diethylaminoethanol

and para-aminobenzoic acid. It is necessary to notice, that para-aminobenzoic acid is competitive antagonist of sulfonamides.

Substituted Amides of Acetanilide

Lidocaine is used for terminal, infiltration, epidural, subarachnoidal, and other types of anaesthesia. The anaesthetic activity of lidocaine is 2.5 times more than novocaine activity. Duration of lidocaine anaesthesia is 2–4 hours. Lidocaine toxicity is equal or slightly higher than toxicity of novocaine. The drug does not have irritative action. Combination of lidocaine with epinephrine solution prolongs duration of anaesthesia and reduces lidocaine toxicity. Symptoms of lidocaine overdose are similar as overdose of novocaine. Lidocaine is not derivative of para-aminobenzoic acid and is not competitive antagonist of sulfonamides. Lidocaine (or trimecaine) may be used in patients intolerant to para-aminobenzoic acid. Besides, lidocaine is the drug of choice for urgent care at ventricular extrasystoles.

Trimecaine activity is 2–3 times higher than activity of novocaine, but at the same time trimecaine is more toxic agent. The duration of anaesthesia caused by trimecaine is about 2–4 hours. The drug is used for conduction and infiltration anaesthesia. The resorptive action of trimecaine is manifested by sedative, hypnotic, antiarrhythmic, and anticonvulsant effects. The use of trimecaine for infiltration and conduction anaesthesia is not accompanied by disorders of cardiovascular system and respiration. Trimecaine overdose can provoke the convulsions.

Bupivacaine hydrochloride (marcaine) is highly active local anaesthetic with long duration of action. The drug is used for conduction and infiltration anaesthesia. Effect develops in 5–10 minutes and lasts up to 7–14 hours (sometimes, up to 24 hours and more). Overdose of marcaine can cause convulsions and suppression of cardiac activity.

Ultracaine (articaine) is drug with fast onset of effect and long duration of action. It is used for infiltration, conduction, subarachnoidal, and lumbar anaesthesia. Toxicity of ultracaine is low.

In stomatological practice, ultracaine is used in combination with epinephrine. The side effects of ultracaine are headache, allergic reaction, and double vision.

Combination of local anaesthetics with hypnotic drugs, general anaesthetics, neuroleptics, and opioid analgesics leads to the increase of anaesthesia. Stimulants of the central nervous system reduce the effect of local anaesthetics.

Astringent Drugs

Astringent drugs coagulate the proteins on the surface of mucous membranes, wounds, and ulcers. Coagulated proteins create the protective film on the damaged surface and protect it from the action of the damaging factors and, also, prevent the absorption of toxins in the blood. Under the influence of astringent drugs, mucosal surface, which commonly has folded structure, is reduced – "contracted" – and small vessels mechanically constrict. Tanning effect develops due to dehydration of submucosal protein layer, its compaction, and the decrease of membrane permeability. These changes result in the reduction of inflammation.

Astringent drugs are classified as follows:

1. Inorganic astringent drugs: *bismuth subnitrate, zinc sulfate, alumen, silver nitrate*, etc.

2. Organic astringent drugs: *tannin, tannalbine (albutannin, albumin tannate);* tinctures, extracts, infusions or decoctions of *oak bark, chamomile flowers, Salvia leaves, Hypericum grass, Aplicata alder, cherry* and *blueberry fruits*, etc.

Inorganic astringent drugs interact with proteins and form albuminates. Depending on concentration and type of the metal, the following effects can develop on the place of drug application: astringent, irritative, or cauterizing. These effects are based on the ability of salts to interact with tissue proteins with the formation of albuminates. The interation with only superficial layers of skin and mucosa is accompanied by formation of dense albuminates preventing the penetration of ions into the deep layers of tissues. In this case, the

astringent effect develops. In case of loose albuminate formation, metal ions penetrate the deep layers of tissues that results in cauterizing effect on the tissue, accompanied by tissue damage (necrosis). Prof. O. Schmiedeberg made up a list of metals based on albuminate density:

Pb, Al, ... Fe, Cu, Zn, ... Ag, Hg.

Metals which are in the left part of this list have mainly astringent and low irritative actions. Metals which are in the right part of the Schmiedeberg's list have cauterizing action and significant antibacterial effect. Metals which are in the middle part of the list can exhibit all these actions in dependence on their concentration.

Lately, inorganic astringent drugs are used reletively seldom.

Organic astringent drugs form with proteins insoluble albuminates. Therefore, their action is restricted by superficial coagulation and does not spread to more deeply located tissues.

Tannin is gallic acid derived from oak apples (*Gallae turcicae*) – growths on the shoots of the Little Asian oak. Tannin is used in solutions and ointments. *Tannalbine* is protein compound of tannin that is used in the treatment for inflammatory diseases of gastrointestinal tracts.

Oak bark, chamomile flowers, Salvia leaves, Hypericum grass, aplicata alder, cherry and *blueberry fruits* and parts of other plants contain significant amount of tannic compounds which provide astringent effect of their galenic preparations (infusions, decoctions, etc.).

Therapeutic applications for astringent drugs are the following:

– acute inflammatory diseases of gastrointestinal tract: gastritis, enteritis, enterocolitis, and stomatitis;

– ulcer disease of stomach and duodenum, chronic gastritis and duodenitis;

– acute bronchitis, laringitis, and tracheitis;

– conjunctivitis;

– uretritis;

– burns, ulcers, traumas of skin and soft tissues;

– acute poisoning by alkaloids and heavy metal salts (0.5 % tannin solution).

Enveloping Agents (Demulcents)

Enveloping agents create colloid solutions in water and provide protection of tissues and endings of sensitive nerves. *Starch slime* and *slime of flax seeds* are most commonly used demulcents. Besides protective action, these drugs exhibit anti-inflammatory and analgesic effects. Enveloping drugs are used to treat the inflammatory diseases of gastrointestinal tract. They are prescribed for oral intake or in enemas. Also, enveloping drugs are used in the treatment for poisoning by acids, alkalies, and other aggressive substances (phenol, solution of bleaching powder, etc.). In this case, enveloping agents protect damaged mucosal surface by colloid film, absorb molecules of irritant, exhibit antiemetic and antidiarrheal effects.

Adsorbing Drugs

Adsorbing drugs are small-pounded biologically inactive powders with high surface activity that are able to adsorb poisons and irritative agents. Adsorbing drugs are *activated carbon (activated charcoal), talc (magnesium silicate), white clay (kaolin), magnesium oxide, zinc oxide, enterosgel, polyphepan,* etc.

Activated cabon is used to treat acute poisoning. The drug adsorbs the poison, reduces its absorption by intestine, and decreases the irritation of intestinal mucous membrane. At poisoning, water suspension of 20–30 g of activated carbon is taken orally or used for gastric lavage. A dose of 1–3 g of activated carbon is taken orally 3–4 times a day to treat flatulence.

Other adsorbing drugs are used in the treatment for different poisoning and intestinal diseases accompanied by putrefaction and flatulence. *Polyphepan* also exhibits cholesterol-lowering effect due to reduction of its intestinal absorption. It is necessary to notice, that long-time intake of adsorbing drugs leads to deficiency of vitamins, lipids, proteins and other vital-essential substances in the body.

Powders, ointments or pastes containing adsorbting agents (talc, magnesium oxide, and zinc oxide) are commonly used to treat damaged humid skin surface.

Besides, there are special sorbents used for hemosorption (elimination of toxins from the blood), lymphosorption, plasmosorption, etc. Presently, many resins with high cation- and

anion-exchange capacity are used for hemosorption. This blood purification method is used in the treatment of some autoimmunic diseases and allows removing antigen-antibody complexes and complements from the blood.

Irritative Drugs

Irritative drugs excite the endings of sensory nerves and cause reflex and local changes which improve blood supply and trophicity of tissues. The group of irritative drugs includes such agents as *sinapisms (mustard plasters), turpentine, camphor, ammonia solution,* etc.

Mustard plasters are one of the most popular irritative drugs. For preparation of mustard plasters, fat-free mustard seed powder is applied on the sheet of thick paper. Before the use, sinapisms should be moistening with warm water (not more 40 °C). Mustard contains glycoside sinigrin and enzyme myrosinase. At temperature about 40 °C, activated myrosinase cleaves sinigrin with formation of allyl isothiocyanate – mustard etheric oil with irritative activity. It is necessary to notice, that hot water (more than 40 °C) intactivates myrosinase, therefore mustard plasters moistened by hot water lack irritative activity. Sinapisms are used in the treatment for respiratory diseases, angina pectoris, neuralgia, and sore muscles (myalgia). Mustard plasters are applied on the site of skin that receives sensory innervation from the same segment of spinal cord as diseased organ. Inflammatory focus in diseased organ is source of painful irritations which permanently enter the corresponding segment of spinal cord and from there – to the central nervous system. It leads to the formation of pathological dominant focus in the CNS. Mustard plaster irritates corresponding part of skin with formation of new flow of nerve impulses to CNS. It creates the new dominant focus of excitation that results in inhibition of pathological focus. Due to such mechanism, painful sensations are significantly reduced. An irritation of the corresponding parts of skin is accompanied by vasodilation and improving the blood supply both in the irritated skin and in the corresponding inner organ. It favours the reduction of inflammation. Thus, the use of irritative agents leads to analgesic and trophic effects.

Turpentine is obtained by distilling galipot from pine trees. The main active substance of turpentine is lipid-soluble α-pinene that

easily penetrates through epidermis and irritates the sensory nerve endings. Turpentine is used in the treatment for neuralgia, myalgia, and arthralgia.

Menthol is etheric oil of peppermint. Applied on the skin or mucous membranes menthol causes the feeling of cold due to irritation of cold receptors. It results in vasoconstriction and reduction of pain at the site of the menthol application. But, the tone of vessels and smooth muscles of inner organs can decrease due to the reflex mechanism. Menthol (in form of drops, inhalations, or anointments) is used in the treatment for inflammatory diseases of upper respiratory tract. Also, menthol is a component of such drugs as validol and corvalol which are used sublingually or orally to treat heartache due to mild attack of angina pectoris and spasm of bile ducts. To treat rhinitis, neuralgia, myalgia, arthralgia, migraine, and skin diseases with itch, 1–2 % menthol oil solution is used.

Ammonia solution has marked irritative properties. Inhalation of wapors of ammonia solution leads to the irritation of sensory nerves of apper respiratory tract and to the reflex stimulation of respiratory centre. This effect is used to treat syncope. To reduce alcohol intoxication, 5–10 drops of ammonia solution per ½ glass of water is used orally. Also, ammonia solution is used to disinfect surgeon hands.

Some drugs acting on the gastrointestinal tract (amarines, emetic and laxative drugs) and expectorants also have reflex action. Their characteristics are given in the corresponding chapters.

Table 5 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
1	2	3
Anaesthesinum	Orally 0.3 g; rectally 0.05–0.1 g; on the skin 5–10 % ointment	Powder; tablets 0.3 g; suppositories 0.05 or 0.1 g; 5 % ointment
Novocainum	For infiltration anaesthesia – 0.25–0.5 % solution; for conduction anaesthesia – 1–2 % solution; for terminal anaesthesia – 10–20 % solution and 5–10 % ointment; rectally 0.1 g	Ampoules 0.25 % and 0.5 % solution – 1, 2, 5, 10 and 20 ml; 1 % and 2 % solution – 1, 2, 5, and 10 ml; vials 200 or 400 ml of 0.25 % or 0.5 % solution; suppositories 0.1 g; 5 % and 10 % ointments
Trimecainum	For infiltration anaesthesia – 0.125–0.5 % solution; for conduction anaesthesia – 1–2 % solution; for terminal anaesthesia – 2–5 % solution; for spinal anaesthesia – 5 % solution	Ampoules 10 ml of 0.25 % solution; 2, 5, or 10 ml of 0.5 % or 1 % solution; 1, 2, 5, or 10 ml of 2 % solution; 1 or 2 ml of 5 % solution
Lidocainum	For infiltration anaesthesia –0.25 % or 0.5 % solution; for conduction anaesthesia – 0.5–2 % solution; for terminal anaesthesia – 1–5 % solution	Ampoules 10 or 20 ml of 1 % solution; 2 or 10 ml of 2 % solution; 2 ml of 10 % solution
Tanninum	For oral, nasal, pharyngeal rinsing, and throat gargling – 1–2 % water or glyceric solutions; for application on injured surfaces – 3–10 % solution or ointment; for gastric lavage – 0.5 % solution	There are no made forms at the plant. Pharmacist prepares these forms (the prescriptions can be written in short or full forms)

Continuation of the table 5

1	2	3
Bismuthi subnitras	Orally – 0.25–0.5 g; on the skin – 5–10 % ointment and aspersion	Powder; tablets 0.25 or 0.5 g; 10 % ointment
Carbo activatus	Orally – 1–2 g to treat meteorism; 20–30 g to treat poisonings	Powder; tablets 0.25 or 0.5 g
Mentholum	For applying on the skin – 0.5–2 % alcoholic solution, 1 % ointment; sublingually 2–3 drops of 5 % alcoholic solution (on a slice of sugar)	1, 2 or 5 % alcoholic solution; 1 % ointment

Step 1. Tasks for Self-Control
Drugs Affecting the Afferent Innervation

1. The patient had received the trauma of an eye due to the hits of the metal shavings. The patient has oedema of the eye, significant hyperemia, and acute pain. The removal of an intraocular foreign body is possible only with local anaesthesia. Choose the drug for local anaesthesia in this case.

A. Benzocaine (anaesthesine).
B. Cocaine.
C. Procaine (novocaine).
D. Trimecaine.
E. Tetracaine (dicaine).

2. An unconscious patient was delivered to the hospital. The doctor gave him the smell of the ammonia solution to bring him to consciousness. What is the type of action, which provides the pharmacological effect of this drug?

A. Etiotropic action.
B. Resorptive action.
C. Reflex action.
D. Local action.
E. Selective action.

3. The conduction anaesthesia was given to a patient before tooth extraction. In several minutes after this, the oedema and hyperemia developed around the injection site; the general weakness and hypotension developed in a patient. Determine the described complication.

A. Allergic reaction.
B. Idiosyncrasy.
C. Tolerance.
D. Tachyphylaxis.
E. Drug dependence.

4. These drugs cause the coagulation of mucous proteins, condense the superficial surface of mucous membranes, and display anti-inflammatory action. What is this group of drugs?

A. Adsorbing drugs.
B. Local anaesthetics.
C. Irritative drugs.
D. Astringent drugs.
E. Covering drugs.

5. This drug has low solubility in water; therefore, it is used for terminal anaesthesia in ointments, pastas, powders, candles. Also, it is prescribed in powders for internal use at stomach pain and vomiting. Indicate this drug.

A. Lidocaine.
B. Procaine (novocaine).
C. Benzocaine (anaesthesine).
D. Tetracaine (dicaine).
E. Trimecaine.

6. A patient has heart pain for some time, which is not connected with physical activity. Call the irritative substance which narrows the vessels of mucous in local use and causes reflex expansion of coronary vessels.

A. Sinapisms.
B. Ammonia solution.
C. Turpentine oil.
D. Camphor.
E. Menthol.

7. Combine operator had received the eye trauma during crop harvest. What local anaesthetic should be used for removal of foreign body from the eye?

A. Sovcaine.

B. Tetracaine (dicaine).

C. Procaine (novocaine).

D. Lidocaine.

E. Trimecaine.

8. A doctor made the sensitivity test to novocaine in a patient before the infiltration anaesthesia. The test is positive. What drug should be used for infiltration anaesthesia to this patient?

A. Cocaine.

B. Novocainamide.

C. Dicaine.

D. Anaesthesine.

E. Lidocaine.

9. A patient with abscess of a shoulder was delivered to the surgery department. During examination a doctor has found out ventricular extrasystoles. What type of anaesthesia is most expedient in this patient?

A. General anaesthesia with ketamine.

B. Local anaesthesia with lidocaine.

C. Spinal anaesthesia with sovcaine.

D. General anaesthesia with hexenalum.

E. General anaesthesia with ether pro narcosis.

10. A patient with acute attack of appendicitis was delivered to a surgery unit. An anaesthesiologist suggested local anaesthesia for operation. But during examination it became clear that the patient had the frequent allergic reaction upon the drugs. Choose the drug which can be used for local anaesthesia in this case.

A. Novocaine.

B. Anaesthesine.

C. Dicaine.

D. Lidocaine.

E. Cocaine.

11. The terminal anaesthesia develops in the result of drug's influence upon the following element of skin and mucous membranes:

A. Derma.

B. Sensitive nervous ending.

C. Epidermis.

D. Hypodermic fatty tissue.

E. Capillaries wall.

12. A patient is in need of the paranefral blockade according to Vishnevsky. What novocaine solution concentration is used in this case?

A. 4–5 %.

B. 0.5–1 %.

C. 1–2 %.

D. 2–4 %.

E. 0.125–0.5 %.

13. A patient with high sensitivity to sulfonamides had appealed to the ophthalmic department with trauma of an eye. What drug should be used for anaesthesia of conjunctiva in this case?

A. Anaesthesine.

B. Novocaine.

C. Lidocaine.

D. Trimecaine.

E. Dicaine.

14. Point out the drug from a group of local anaesthetics which is not desirable to prescribe simultaneously with sulfonamides.

A. Ultracaine.

B. Novocaine.

C. Anaesthesine.

D. Lidocaine.

E. Trimecaine.

15. A doctor has prescribed an ointment "Efcamonum" to a patient. This ointment is an irritative drug according to the mechanism of action. Indicate the case in which "Efcamonum" is contraindicated.

A. Neuritis.

B. Neuralgia.

C. Pain in a joint.

D. Skin injury.

E. Myalgia.

16. The action of novocaine is decreased in areas of inflammation because the disturbance of hydrolysis of novocaine salt and release of active basic substance develop. What is the cause of this phenomenon?

A. Inhibition of oxidative phosphorylation.

B. Local tissue alkalosis.

C. Inhibition of carbonic anhydrase.

D. Activation of succinate dehydrogenase.

E. Local tissue acidosis.

17. A third year student during the practice should put the sinapisms on the back of a patient. For this purpose, he has moistened the sinapisms with very hot water (the temperature is more than 60 °C). In 30 minutes, the student has found out that the skin of the patient has not reddened in the place of applied sinapisms. What is the cause of this phenomenon?

A. Hot water causes activation of MAO.

B. Hot water causes inactivation of mirosine.

C. Hot water causes inactivation of cholinesterase.

D. Hot water causes activation of mirosine.

E. Hot water causes inactivation of MAO.

18. A 25-year-old woman with red and itchy eczematoid dermatitis visits your office. She had a dental procedure one day earlier with administration of local anaesthetic. There are no other data, although she indicated that she had a history of allergic reactions. Which of the following drugs is most likely involved?

A. Procaine.

B. Cocaine.

C. Bupivacaine.

D. Lidocaine.

E. Etidocaine.

19. A patient with an abscess was admitted to a surgical department for operative treatment. During additional examination the ventricular premature beats were detected. What drug is the most expedient for anaesthesia in this case?

A. Ketamine.

B. Halothane (fluothane).

C. Hexenal.

D. Diethyl ether.

E. Lidocaine.

Drugs Influencing Efferent Innervation

Cholinergic Drugs

Cholinomimetic Drugs

The nervous system is divided into two branches: the central nervous system (brain and spinal cord) and peripheral nervous system. Peripheral nervous system is divided into the afferent (or sensory) part and efferent part. The neurons of afferent part bring information from the periphery to the central nervous system. The efferent neurons carry information from the central nervous system to the peripheral tissues. Efferent division includes autonomic system and somatic neurons.

The autonomic nervous system carries impulses from the central nervous system to the inner organs by way of two neuron types. The first neuron is called a preganglionic neuron. Its cell body is located within the central nervous system. Preganglionic neuron makes a synaptic contact in ganglion. The ganglion works as transmitting station between the preganglionic neuron and the second nerve cell called a postganglionic neuron. The endings of postganglionic neurons contact with cells of inner organs. The somatic nervous system travels directly to skeletal muscles without the mediation of ganglia. The somatic nervous system is under voluntary control, whereas the autonomic system is an involuntary one.

Autonomic nervous system is divided into the sympathetic and parasympathetic parts. The preganglionic neurons of the sympathetic nervous system have their cell bodies within the thoracic and lumbar regions of the spinal cord – the thoracolumbar division. The preganglionic neurons of the parasympathetic part have their cell bodies in the brainstem and in the sacral region of the spinal cord – the craniosacral division. The cranial part of the parasympathetic nervous system innervates the head, neck, thorax, and abdomen (the stomach, part of intestine and pancreas). The cranial parasympathetic nerves leave the central nervous system in the oculomotor, facial, glosopharyngeal and vagal cranial nerves. About 75 % of the parasympathetic fibers are contained within the vagus

nerve. The sacral division of the parasympathetic nervous system innervates the remainder of the intestine and the pelvic viscera.

The sympathetic ganglia form two chains of ganglia, which are located laterally to the vertebral column. Because the sympathetic ganglia are located close to the vertebral column, their preganglionic fibers, as a rule, are short. But postganglionic fibers are long since they arise in vertebral ganglia and must travel to the innervated cells of the inner organs. The parasympathetic ganglia are located close to or within the organs innervated by the parasympathetic postganglionic neurons. As a rule, all inner organs receive both the sympathetic and parasympathetic innervation. Sympathetic and parasympathetic systems work in opposition one to another.

Communications between nerve cells as well as between nerve cells and effector organs occur due to the release of the specific chemical substances by nerve terminals. These substances are called neurotransmitters (mediators). The neurotransmitters rapidly diffuse across the synaptic cleft (synapse) between nerve endings and bind with specific receptors on the membrane of postsynaptic cell.

There are two main mediators of autonomic nervous system. They are acetylcholine and noradrenaline (norepinephrine).

There are the following main sites of neurotransmission in the peripheral nervous system:

– parasympathetic and sympathetic ganglia;
– parasympathetic and sympathetic postganglionic neuroeffector synapses;
– skeletal muscle endplates.

Acetylcholine is released in these sites except of most sympathetic neuroeffector synapses. Neurons which release acetylcholine are called cholinergic neurons.

Norepinephrine is released in most of sympathetic postganglionic neuroeffector synapses. Neurons which release norepinephrine are called adrenergic neurons.

It is necessary to notice, that some sympathetic postganglionic neurons are cholinergic. Thus, sympathetic postganglionic neurons

innervating the sweat glands and some blood vessels in skeletal muscle release acetylcholine. But anatomically they are sympathetic neurons.

Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidneys, pilomotor muscles, and sweat glands are innervated only by sympathetic system. Blood pressure is also controlled mainly by sympathetic nervous system.

Adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers of the sympathetic system. The adrenal medulla cells (chromaffin cells) are homologous with sympathetic postganglionic neurons. Therefore, adrenal medulla may be considered as a modified sympathetic ganglion. The adrenal medulla secretes two hormones. The main medullary hormone is adrenaline. Second is noradrenaline that is also the primary mediator of sympathetic postganglionic neurons. General activation of the sympathetic system due to stress, fear, or anxiety is accompanied by increased secretion of adrenal medullary hormones. The CNS regulates the secretory activity of the adrenal medulla.

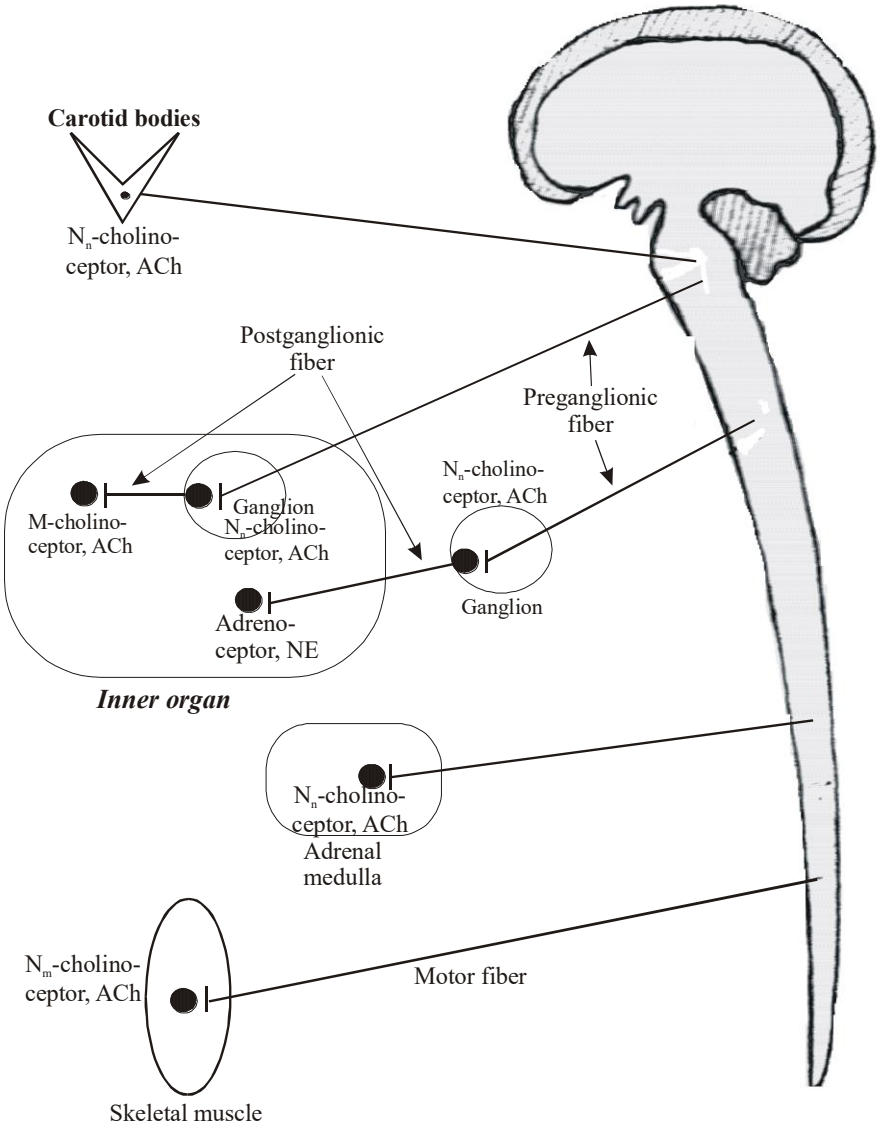

Figure 3 – The scheme of efferent innervation

The activity of autonomic nervous system may be changed by means of different medicines. Drugs affecting the autonomic nervous system are divided into two groups corresponding to the type of neuron involved in their mechanism of action. There are cholinergic and adrenergic drugs. The cholinergic drugs act on the receptors that are activated by acetylcholine. The adrenergic drugs act on receptors that are stimulated by norepinephrine.

Drugs which influence parasympathetic nervous system are divided into cholinomimetic drugs (they excite cholinergic receptors) and cholinoblockering drugs (they bind with cholinergic receptors and prevent its excitation).

The main localization sites of cholinergic synapses are:

– both sympathetic and parasympasetic ganglia;
– inner organs near the endings of the parasympathetic postganglionic fibers;
– medullary substance of the adrenal glands;
– skeletal muscles;
– carotid glomeruli;
– vessels of skeletal muscles;
– central nervous system.

Structure of cholinergic synapse is the following. As well as all other synapses, cholinergic synapse consists of presynaptic membrane, synaptic cleft, and postsynaptic membrane containing cholinergic receptors.

Transmission of nervous impulses in cholinergic synapse involves the following processes.

Acetylcholine synthesis. Acetylcholine is synthesized from choline and acetyl CoA in the cytosol of preganglionic neuron's endings. Synthesis of acetylcholine is catalyzed by choline acetyltransferase:

$$CH_3\text{-}CoA + HOCH_2\text{-}CH_2N(CH_3)_3 \xrightarrow{\text{choline acetyltransferase}} CH_3\text{-}COOCH_2CH_2N(CH_3)_3.$$

Acetylcholine storage. The acetylcholine is packaged into the vesicles by means of active transport. Synthesized acetylcholine is distributed in three pools:

– associated pool that is unsuitable for immediate mobilization;

– weakly-associated pool released during work;

– "hot" pool that is able immediately to be released into synaptic cleft.

Acetylcholine release. Presynaptic membrane contains many diffusion channels for acetylcholine. Incoming nervous impulse leads to the release of Ca^{2+} that result in acetylcholine release from the vesiculs into the synapse.

Acetylcholine interaction with cholinoceptors. Released acetylcholine diffuses across the synaptic space and binds to postsynaptic receptors on the target cell. This binding is possible due to physic-chemical affinity of acetylcholine to cholinoceptor. Interaction of acetylcholine with cholinergic receptors results in certain biological response in the cell.

Nowadays, pure forms of cholinergic receptors are isolated from the cellular membrane. It was found that these receptors are not homogeneous and characterized by certain conformational differences. These differences are insignificant for acetylcholine binding, but they are important for interanction between receptors and different pharmacological agents.

Some cholinoceptors are selectively activated by muscarine (poisonous alkaloid of fly-agaric) and blocked by atropine (belladonna alkaloid). These receptors are called muscarinergic cholinoceptors or M-cholinoceptors. Another type of cholinergic receptors is selectively activated by small doses of nicotine and blocked by its high doses. These receptors are called nicotinergic cholinoceptors or N-cholinoceptors (H. Dale and S. Anichkov). In more detail, the characteristicas of different types of cholinoceptors are given below.

Acetylcholine inactivation. After the interaction with cholinoceptors, acetylcholine is quickly metabolized by the enzyme

acetylcholinesterase. This enzyme cleaves acetylcholine to choline and acetate:

$$CH_3\text{-}COOCH_2CH_2N(CH_3)_3 \xrightarrow{\text{acetylcholinesterase}} CH_3\text{-}COOH + HOCH_2\text{-}CH_2N(CH_3)_3.$$

Acetylcholinesterase accelerates the hydrolysis of acetylcholine in millions of times. Fast acetylcholine hydrolysis leads to lowering of the mediator concentration and a rapid dissociation of the mediator from its receptors. Choline undergoes the reuptake by the nerve terminals, where it is used for the further acetylcholine synthesis.

M-cholinoceptor is the complex receptor system that contains the following elements:

– superficial part of receptor that recognizes the mediator;

– G-protein that is located on the inner surface of cell membrane;

– enzyme (adenylyl cyclase or phosphorylase C) or ionic channel.

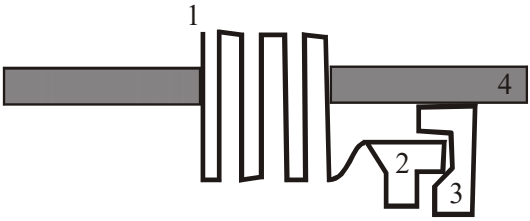

Figure 4 – M-cholinoceptor model
(according to V. Vinogradov)

1 – superficial part of receptor that recognizes acetylcholine; it consists of sites of long polypeptide chain which protrude above the membrane surface and permeate it, like a serpentine, 7 times;

2 – G-protein; there are G_i-proteins inhibiting adenylyl cyclase, G_s-proteins stimulating adenylyl cyclase, G_q activating phospholipase C, G_o opening ionic channel, and other G-proteins;

3 – membrane enzyme or ionic channel;

4 – cell membrane

Transmission of signal through M-cholinoceptor to intracellular effectors (enzymes) are carried out in several steps:

– acetylcholine interacts with superficial part of receptor;

– receptor activates G-protein;

– G-protein changes functional activity of membrane enzyme or ionic channel.

Five subtypes of M-cholinoceptors are known presently: M_1-, M_2-, M_3-, M_4-, and M_5-cholinoceptors. These subtypes of muscarinic receptors are heterogeneously distributed in the human body.

Table 6 – Predominant localization and functional role of different subtypes of M-cholinoceptors

Cholinoceptor subtype	Localization	Effect of activation
1	2	3
M_1-cholinoceptors (located outside of the synapse)	Membranes of the cells of both parasympathetic and sympathetic ganglia (receptors with modulating function)	Slow depolarization of ganglionic neurons
	Endothelial cells of vessels, mainly in skeletal muscles, skin, subcutaneous tissue	Secretion of endothelial relaxing factor and vasodilation
Postsynaptic M_2-cholinoceptors	Endings of postganglionic parasympathetic neurons in the heart	Automatism reduction (bradycardia), slow down of conduction, decrease of atrial contractility
Presynaptic M_2-cholinoceptors	Presynaptic membrane of the endings of parasympathetic and sympathetic nerves	Deceleration of the mediator release (acetyl-choline and noradrenaline)

Continuation of the table 6

1	2	3
Postsynaptic M_3-cholinoceptors	The endings of postganglionic parasympathetic nerves in the smooth muscles of urinary tract, gastrointestinal tract, bronchi, and eye	Contraction
	The endings of postganglionic parasympathetic nerves in the exocrine glands (salivary, nasopharyngeal, bronchial, stomach, and intestine glands)	Elevation of secretion
	The endings of postganglionic sympathetic nerves in the sweat glands	Elevation of secretion
M_1-, M_2-, M_3-, M_4-, M_5-cholinoceptors	Central nervous system (cortex, subcortical structures, reticular formation, etc.)	Different effects

M_3- and M_1-cholinoceptors are coupled with G_q-proteins. Their excitation by acetylcholine leads to activation of phospholipase C and the release of intracellular calcium.

Activation of M_2-receptors through G_i-proteins inhibits adenylyl cyclase and simultaneously activates potassium channels through G_o-proteins. Increased potassium outward current from the cells hyperpolarizes the cellular membrane and decreases excitability of cells. The inhibition of adenylyl cyclase decreases cellular cAMP (cyclic adenosine monophosphate) level.

Activation of presynaptic M_2-cholinoceptors inhibits the following release of acetylcholine into the synaptic cleft.

N-cholinoceptor consists of 5 polypeptide subunits (two α-, β-, γ- and δ-subunits) located surrounding a sodium channel.

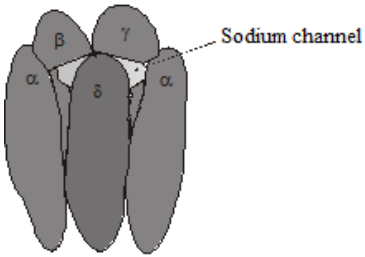

Figure 5 – N-cholinoceptor model (according to J. Kistler, R. M. Stroud)

For understanding the mechanism coupling N-cholinoceptor activation with cellular function, it is necessary to remember that external surface of membrane at rest is charged positively, but internal surface is charged negatively. This charge is due to difference in distribution of cations: intracellular potassium concentration is higher than its concentration in the environment surrounding the cell. Vice versa, sodium concentration is higher in the environment surrounding the cell. Sodium ions drag the anions which are accumulated near internal surface of membrane and cause its negative charge.

Acetylcholine binds with two α-subunits that leads to opening of sodium channel. Inward sodium current causes the membrane depolarization and the occurrence of action potential. In skeletal muscles, an action potential causes the activation of Ca^{2+}-channels that is accompanied by the increase of cytoplasmic calcium concentration and the following muscular contraction.

It is necessary to notice, that nicotinic receptors of vegetative ganglia differ from those of the neuromuscular junction. Thus, ganglionic receptors are selectively blocked by benzohexonium, whereas cholinergic receptors in skeletal muscles are selectively blocked by tubocurarine. Ganglionic receptors are called N_n-cholinoceptors, but the neuromuscular junction receptors – N_m-cholinoceptors.

Drugs which affect the impulse transmission in the cholinergic synapses are called cholinergic drugs. They are divided into the cholinomimetic (agents stimulating the cholinoceptors or leading to their excitation) and the cholinolytic drugs (agents blocking the cholinoceptors). Each of these groups is classified into subgroups depending on the influence upon the different types of cholinoceptors.

Classification of Cholinergic Drugs

I. Cholinomimetic drugs.

1. M-, N-cholinomimetic drugs with direct action: *acetylcholine* and *carbacholine*.

2. M-cholinomimetic drugs with direct action: *pilocarpine* and *aceclidine*.

3. N-cholinomimetic drugs with direct action: *nicotine, lobeline,* and *cytitonum*.

4. Indirectly acting M-, N-cholinomimetic drugs or cholinesterase inhibitors: *galantamine, physostigmine, proserinum (neostigmine), pyridostigmine, rivastigmine, oxazylum (ambenonium), distigmine,* and *armin*.

II. Anticholinergic drugs.

1. M-cholinolytic drugs: *atropine sulfate, scopolamine, platyphyllin, metacinum, ipratropium bromide, pirenzepine, homatropine,* and *tropicamide*.

2. N-cholinolytic drugs.

2.1. N_n-cholinolytic drugs (ganglion blocking drugs): *benzohexonium, pentaminum, hygronium, arfonade, pirilenum,* and *pachycarpine*.

2.2. N_m-cholinolytic drugs (peripheral myorelaxants): *tubocurarine, pipecuronium, pancuronium, dithylinum,* and *dioxonium*.

M-, N-Cholinomimetics with Direct Action

M-, N-cholinimetic drugs with direct action are *acetylchiline* and *carbacholine*.

Acetylcholine is a quaternary ammonium compound that cannot penetrate membranes. Acetylcholine excites both M- and N-cholinoceptors. In case of oral intake, acetylcholine is destroyed before absorption in the blood. Subcutaneously administered acetylcholine is quickly hydrolyzed in the blood. Therefore, resorptive action of acetylcholine is observed only after its intravenous administration. In this case, the excitation of M-choliceptors is predominant.

The following effects of M-cholinoceptors stimulation are observed.

Heart. Activation of M_2-receptors by acetylcholine increases the potassium permeability and reduces cAMP levels, that results in the deceleration of depolarization and reduction of the excitability of sinoatrial and atrioventricular nodes. It results in marked bradycardia and a deceleration of atrioventricular conduction. Very high doses of acetylcholine, as other M-chlolinergic agonists, can cause lethal bradycardia and atrioventricular blockage.

Vascular tone and blood pressure. Due to stimulation of M-cholinoceptors of vascular endothelial cells, acetylcholine causes vasodilatation and reduces the blood pressure. M-cholinoceptors excitation stimulates the synthesis and release of nitric oxide by the endothelial cells. Nitric oxide diffuses to vascular smooth muscle cells and activates guanylyl cyclase that leads to the increase of cGMP (cyclic guanosine monophosphate) synthesis and relaxation of vascular smooth muscles. It is necessary to notice, that the the resistance vessels are not innervated by cholinergic neurons, and the physiological role of the endothelial M-cholinoceptors is unknown. But, activation of these receptors by directly acting M-cholinomimetic drugs leads to marked hypotension.

Exocrine glands. Owing to excitation of M_3-cholinoceptors, acetylcholine increases secretion of all exocrine glands: salivary, sweat, lacrimal, nasopharyngeal, bronchial, gastric, etc.

Smooth muscles. Acetylcholine increases the bronchial tone, stimulates motility and tone of stomach, intestine, gallbladder, bile ducts, and bladder.

Eye. Acetylcholine causes contraction of the iris sphincter and ciliary muscles. Contraction of the iris sphincter muscle leads to the decrease of the pupil diameter (miosis). The intraocular pressure is lowered because the pupil sphincter contraction provides opening of the spaces of the iris angle (Fontana's spaces). Due to this, the outflow of the aqueous humour from the anterior chamber of the eye into the venous sinus of the sclera (the Schlemm channel) is increased. Contraction of the ciliary muscle reduces the tension of the suspensory ligaments stretching and flattening the lens. It results in the increase of the lens curvature. The lens focuses for near vision. This phenomenon is called the spasm of accommodation.

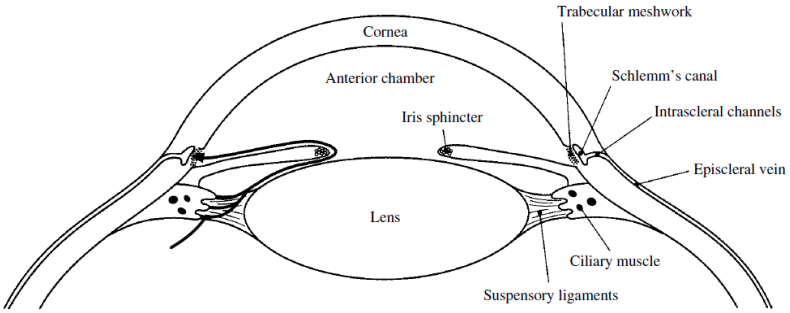

Figure 6 – Major pathways for aqueous humor outflow as a result of ocular smooth muscle contraction caused by direct and idirect cholinomimetics (by Craig C., Stitzel R.E., 2003)

The sensitivity of N-cholinoceptors to acetylcholine is significantly less, than sensitivity of M-cholinoceptors. Therefore, the effects of their excitation are observed against the background of the preliminary administration of M-cholinergic antagonist (e. g., atropine). In this case, intravenous acetylcholine administration results in the elevation of blood pressure. It is due to stimulation of N-cholinoceptors of sympathetic ganglia and chromaffinic cells of

adrenal medulla releasing adrenaline. Partly, this effect is also the result of excitation of N-cholinoceptors of carotid bodies that provides the increase of tone vasomotor centre. Marked respiratory stimulation, observed after intravenous acetylcholine administration, is also due to the stimulation of N-cholinoceptors of carotid bodies. Besides, acetylcholine increases the vasopressin release by posterior pituitary and improves the neuromuscular transmission in skeletal muscles.

Acetylcholine is rapidly hydrolyzed by cholinesterase. Subcutaneously administered acetylcholine acts 5–15 min. Acetylcholine practically does not have therapeutic value. Sometimes, it is used for the cardiac arrest during operations with artificial circulation or administered intravenously in the treatment for frostbite of the extremities.

Carbacholine (Carbachol) is synthetic ester of choline and carbamic acid. Its duration of action is 1–1.5 hours. Because the drug excites both M- and N-cholinergic receptors, its effects are like the effects of acetylcholine. Ocular films or eye drops with carbacholine is used to treat the open-angle glaucoma which is resistant to pilocarpine.

Cholinesterase Inhibitors

Cholinesterase inhibitors bind and inhibit the activity of both acetylcholinesterase and butyrylcholinesterase (pseudocholinesterase, or plasma cholinesterase).

These drugs are classified as follows:

1. Cholinesterase inhibitors of reversible action: *galantamine, physostigmine, oxazylum (ambenonium), proserinum (neostigmine), rivastigmine (Exelon), pyridostigmine,* and *distigmine*.

2. Cholinesterase inhibitors of irreversible action: *armin*.

Also, numerous phosphorus organic compounds as insecticides (carbophos, chlorophos, dichlophos, etc.) and warfare agents (sarin, soman, etc.) are irreversible inhibitors of cholinesterase.

The drugs of reversible action reversibly inactivate the enzyme due to formation of the unstable bond with it. The irreversibly-acting

drugs covalently bond to cholinesterase; therefore, the inhibition of enzyme has the irreversible character. It is necessary to notice, that this covalent bond is slowly hydrolyzed by water (about 20 days).

Acetylcholinesterase is membrane bound enzyme located both pre- and postsynaptically in the cholinergic nerve endings. Cholinesterase molecule has two centres interacting with acetylcholine: the anionic centre and the esterase centre. The anionic centre binds to the positively charged quaternary ammonium group of acetylcholine. The esterase centre binds to carbon of carbonyl group of acetylcholine. This leads to hydrolysis of acetylcholine. Acetylcholine hydrolysis lasts about 150 microseconds. It is one of the fastest enzymatic reactions that is known nowadays.

Cholinesterase inhibitors can bind ether anionic centre (edrophonium) or esterase centre (most phosphorus organic compounds). Some drugs bind to both centres (proserinum). The enzyme inhibition leads to accumulation of acetylcholine in synapses. It results in the excitation of both M- and N-cholinoceptors. But at resorptive action of cholinesterase inhibitors, first, the effects of activation of M-cholinoceptors are observed:

– miosis;
– increased salivation;
– increase of bronchial tone;
– bradycardia that is replaced by tachycardia;
– increase of intestinal motility and tone;
– hypotension that is replaced by elevation of blood pressure;
– stimulation of uterine contraction;
– increase of bladder tone.

In some cases, effects of cholinesterase inhibitors differ from effects of M-cholinomimetics: tachycardia is observed after bradycardia and lowering of blood pressure is replaced by the pressor effect. It is due to the later acetylcholine activation of N-cholinergic receptors of sympathetic ganglia and adrenal medulla. Acetylcholine accumulation near N_m-cholinoceptors of skeletal muscles leads to facilitation of neuromuscular transmission. It is necessary to notice,

that high doses of cholinesterase inhibitors cause muscle twitching replaced by blockage of neuromuscular transmission.

Presently, there are evidences that together with the blockage of enzyme, cholinesterase inhibitors (e. g., proserinum) are able directly to bind and excite the cholinergic receptors. The direct activation of cholinergic receptors plays a secondary role in action of cholinesterase inhibitors.

Physostigmine is an alkaloid of plants and a tertiary amine that penetrates in the central nervous system. The drug acts about 2–4 hours. Eye drops of physostigmine are used to treat glaucoma. Physostigmine is also used to treat the overdoses of M-chlolinergic antagonists (atropine, scopolamine, etc.). The drug is used to treat Alzheimer's disease[1)], craniocerebral traumas, cerebral hemorrhages, and residual effects after poliomyelitis. It should be noticed that physostigmine can produce cardiac arrhythmias and other serious toxic effects which restrict its clinical use.

Rivastigmine (Exelon) is a semisynthetic derivative of physostigmine. The drug inhibits central nervous system acetylcholinesterase 10 times stronger than the corresponding peripheral tissue enzyme. Rivastigmine is used to treat Alzheimer's disease and demencias associated with Parkinson's disease. Available dosage forms of rivastigmine include capsules, oral solution, and a transdermal patch. Common side effects are nausea, vomiting, insomnia, vertigo, agitation, confusion, and anorexia.

Galantamine is alkaloid of Woronow's snowdrop. It is tertiary amine that penetrates central nervous system. Therapeutic indications of galantamine are like physostigmine. But galantamine is not used in the glaucoma treatment due to its irritative action that causes conjunctival oedema.

At the therapy of the damages of central nervous system (traumas, strokes, poliomyelitis, etc.), physostigmine and galantamine are prescribed after liquidation of the acute symptoms; when residual disturbances are persisting due to stable inhibition in CNS.

[1)] Alzheimer's disease or senile dementia is a slowly developing neurodegenerative disease that is characterized by the memory loss and cognitive dysfunction.

Cholinesterase inhibitors stabilize acetylcholine concentration, and synaptic transmission is improved; that diminishes the residual symptoms.

Proserinum is a synthetic polar compound and, therefore, does not penetrate in the central nervous system. Its stimulative effect on skeletal muscles is greater than that of physostigmine. The duration of action of proserinum is 2–4 hours.

The duration of action of *pyridostigmine* is longer than that of proserinum.

Except the treatment of some diseases of the central nervous system, there are the following therapeutic indications for cholinesterase inhibitors:

1. Glaucoma. Cholinesterase inhibitors are applied topically in forms of eye drops or eye ointment. The use of 0.25–1 % physostigmine solution causes the marked reduction of intraocular pressure. It is commonly used to treat acute glaucoma in cases when pilocarpine is ineffective. Proserinum (0.5 % solution) and armin (0.01 % solution) are also used in the treatment of glaucoma. As mentioned above, galantamine is not used for this purpose.

2. Postsurgical atony of intestine and bladder. As a rule, 0.25–0.3 ml 0.5 % proserinum solution is injected subcutaneously every 30–60 minutes up to the occurrence of peristalsis. If patient's condition allows, proserinum may be taken orally 2–3 times a day. If long-time treatment is necessary, pyridostigmine is preferable. It is administered intramuscularly or taken orally 1–3 times a day.

3. Residual muscular relaxation after the use of non-depolarizing myorelaxants (e. g., tubocurarine). The drug of choice is proserinum.

4. Peripheral paralysis of skeletal muscles and myasthenia gravis. Cholinesterase inhibitors poorly penetrating in the central nervous system are preferable in these cases: proserinum, pyridostigmine, and distigmine. The therapeutic regimen is selected individually.

Side effects of these drugs are hypersalivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, bronchospasm, and bradycardia.

Cholinesterase inhibitors are contraindicated in bronchial asthma, organic heart diseases with disorders of conduction, and pregnancy.

Acute poisoning by irreversibly-acting cholinesterase inhibitors is frequent because organophosphorus compounds are widely used as agricultural and household insecticides. Many of these substances are extremely toxic and were developed by the military as nerve agents. Acute poisoning is manifested by the following symptoms: gastrointestinal distress (hypersalivation, nausea, vomiting, and diarrhea), bronchospasm and increased bronchial secretion, bradycardia that is replaced by tachycardia, AV-block, hypotension, miosis, sweating, and disturbances of skeletal muscles function (successive incoordination, muscle cramps, weakness, fasciculation, and paralysis). The symptoms of central nervous system damage include agitation, dizziness, convulsions, and mental confusion. Death usually results from paralysis of skeletal muscles required for respiration, or owing to the cardiac arrest. Depending on the severity of poisoning, death occurs in several minutes or hours (up to a day). The urgent care includes the administration of atropine and cholinesterase reactivators, elimination of poison from the organism, and symptomatic therapy. To reduce psychomotor excitement, the drugs inhibiting central nervous system (e.g., aminazine, diazepam, etc.) are used.

In 1951, it was found that covalent bond between organophosphorus compound and cholinesterase is slow hydrolysed by water. Substances, which contain oxime group (-N=N-OH) in molecules, accelerate this reaction. Drugs with such action are called cholinesterase reactivators. The mechanism of restoration of enzyme activity is based on the reactivator ability to bind to organophosphorus residue and to cleave it from cholinesterase. But, "poisoned" enzyme quickly is "aging" and lost the ability to be reactivated. Therefore, the administration of reactivator should be as early as possible. There are the following cholinesterase reactivators: *dipyroxime* (*trimedoxime bromide*), *isonitrosine*, *alloxime*, and *pralidoxime*. These drugs are administered parenterally.

M-Cholinomimetic Drugs

An ancestor of M-cholinomimetics is muscarine. But it does not have practical use in medicine and is used for toxicological investigations only. M-cholinomimetic drugs are *pilocarpine* and *aceclidine*. The mechanism of action of these drugs is associated with direct stimulation of all sybtypes of M-cholinoceptors: M_1, M_2, and M_3. As mentioned above, M-cholinoceptors are in cellular membranes near postganglionic parasympathetic nerves:

– in all inner organs receiving parasympathetic innervation;

– in the salivary glands and smooth muscles of vessels receiving sympathetic but cholinergic innervation;

– in the central nervous system (reticular formation, new cortex, limbic system, hippocampus, etc.).

Because M-cholinoceptors belong to effector cells, the activity of direct M-cholinomimetics persists and even became higher due to denervation or degeneration of the nerve.

Effects of M-cholinomimetics are very similar to effects of cholinesterase inhibitors and M, N-cholinomimetics.

Because the cardial branches of vagus mainly innervate sinoatrial and atrioventricular nodes of heart (ventricles are not innervated by parasympathetic innervation), the action of M-cholinomimetics is directed upon the function of these nodes. The excitation of M_2-cholinoceptors of sinoatrial node leads to bradycardia. Due to that, cardiac output and blood pressure are reduced. Intravenous administration of M-cholinomimetics can result in sudden cardiac arrest. Therefore, intravenous administration of M-cholinomimetics is not practiced.

Excitation of M_2-cholinergic receptors of conductive system by M-cholinomimetics also results in slow down of conduction. This phenomenon is most marked in the atrioventriculalar node. M-cholinomimetics can provoke atrioventricular blockages of different degrees.

M-cholinomimetics reduce blood pressure due to:

– reduction of heart work;

– excitation of M-cholinergic receptors in vessels of skeletal muscles (these receptors are innervated by sympathetic cholinergic nervous fibers);

– excitation of M-cholinoceptors of sweat glands which are also innervated by sympathetic cholinergic fibers.

Sweat glands secrete proteolytic enzyme kallikrein that synthesizes bradykinin. Bradykinin causes the dilation of arterioles and capillaries of skin and subcutaneous tissue that promotes the hypotension.

Other effects of M-cholinomimetics include miosis, lowering of the intraocular pressure, the spasm of accommodation, the increase of smooth muscle tone (bronchi, gastrointestinal tract, biliferous and urinary tracts, and uterus), hypersecretion of bronchial, digestive, and lacrimal glands.

Pilocarpine is alkaloid derived from the leaves of tropical plant Pilocarpus jaborandi. Pilocarpine is characterized by more marked influence upon exocrine gland secretion than upon the tone of smooth muscules. After pilocarpine injection, sweat glands secrete during 3–4 hours about 3 litres of sweat. General loss of liquids by human body is about 5–6 litres. It results in serious dehydration. Therefore, resorptive effects of pilocarpine are not used in medicine. However, pilocarpine is widely used in the treatment of glaucoma. It is the drug of choice in the emergency lowering of intraocular pressure in glaucomatous crisis. Pilocarpine is used as 1–5 % eye drops (duration of action – 4–8 hours), 1–5 % eye ointment, eye membranules on the polymer base that slowly dissolve in lacrimal fluid (act to 24 hours), and insoluble membrane systems that slowly release pilocarpine (*Ocusert*). Duration of Ocusert action is 5–7 days.

It is necessary to notice, that pilocarpine can penetrate through the blood-brain barrier and affects the central nervous system function. To escape the penetration of cholinomimetics into the blood stream after its topical application into the eye, the mechanical pressure is applied to the lacrimal duct.

Aceclidine is synthetic compound. It is used in the treatment of glaucoma, postsurgical intestinal and bladder atony. For treatment of

intestinal and bladder atony, 1–2 ml of 0.2 % aceclidine solution is administered subcutaneously. If necessary, administration can be repeated 2–3 times with intervals 30–60 minutes. Also, aceclidine is sometimes used in the treatment for uterine atony and uterine bleeding in the postpartum period.

In rare cases, when hemodialysis is impossible, pilocarpine may be administered to treat acute renal insufficiency. From 10 to 15 mg of pilocarpine is administered subcutaneously considering possible side effects; 2–3 litres of water, sodium chloride, nitrogen compounds are excreted from the body for 2 hours. Undesirable effects may be stopped by atropine administration.

M-cholinomimetics are contraindicated in bronchial asthma, disorders of the cardiac conduction, ischemic heart disease, hyperthyroidism, Parkinson disease, epilepsy, hyperkynesia, and pregnancy.

The poisonings by M-cholinomimetics are most commonly caused by fly-agaric. The typical symptoms of poisoning are nausea, abdominal cramps, diarrhea, salivation, hypotension with reflex tachycardia, cutaneous vasodilation, sweating, miosis, spasm of accommodation, macropsia, and bronchoconstriction. Agitation and convulsions are also possible. As a rule, death occurs due to paralysis of respiratory centre. The urgent aid includes gastric lavage and administration of atropine that eliminate all symptoms of poisoning.

N-Cholinomimetic Drugs

Group of N-cholinomimetics includes *nicotine, lobeline* and *cytitonum*.

These drugs selectively excitate N_n-cholinergic receptors. N_n-cholinoceptors are in the carotid bodies, adrenal medulla, vegetative ganglia, and central nervous system.

Nicotine is the alkaloid of the plant tobacco (Nicotiana tabacum and Nicotiana rustica). As a rule, a cigarette contains 6–8 mg of nicotine. About 60 mg of nicotine results in the acute lethal poisoning. More than 60 % of nicotine inhaled while smoking is absorbed into the blood. Nicotine has no therapeutic value. It has only toxicological significance. Nicotine is one of the most widely used stimulants of the

central nervous system. Chronic nicotine consumption results in abuse. Except nicotine, cigarette smoke contains carbon monoxide, phenol, and toxic tars. Therefore, chronic smoking results in the serious risk of cardiovascular disease, various cancers, and diseases of the gastrointestinal tract (ulcers, gastritis).

The peripheral effects of nicotine are complex.

Low doses of nicotine stimulate N_n-cholinoceptors of both parasympathetic and sympathetic ganglia. Stimulation of sympathetic ganglia increases blood pressure and heart rate. Nicotine decreases coronary blood flow. Stimulation of parasympathetic ganglia increases the motility of gastrointestinal tract. Low doses of nicotine stimulate the central nervous system activity and cause some euphoria. Nicotine stimulates the release of dopamine, endogenous opioids and glucocorticoids. The high doses of nicotine provide the ganglionic blockade and cause marked hypotension. Lethal doses of nicotine paralyse respiratory centre.

Because nicotine is highly-lipid soluble substance, it easily penetrates through the placental barrier and is dangerous for fetus. Also, nicotine is secreted in the milk of lactating women.

Chronic smoking is accompanied by fast development of tolerance to the toxic effects of nicotine. Also, chronic consumption of nicotine rapidly leads to the drug dependence (abuse). Withdrawal syndrome is manifested by such symptoms as irritability, anxiety, restlessness, difficulty in concentrating, headaches, and insomnia.

Lobeline and *cytitonum* are used in medicinal practice. The practical importance of these drugs is their ability to excitate N_n-cholinoceptors of the carotid glomeruli that leads to the reflex stimulation (through Hering's nerve which is a branch of glossopharyngeal nerve) of the respiratory and vasomotor centres of medulla oblongata.

These drugs are analeptics of reflex action and used as breathing stimulants. Their intravenous administration leads to potent but short effect (2–5 min). The respiratory centre depression caused by CNS depressants (barbiturates, morphin, etc.) results in the loss of its sensitivity to CO_2. In such conditions, the reflex stimuli from the vascular chemoreceptors have predominant influence upon respiratory centre. Thus, keeping the reflex excitability of respiratory centre allows to use N-cholinomimetics for restoration of breathing.

It should be noticed that in case of intravenous administration, minimal doses of N-cholinomimetic stimulate respiratory centre. At the same time, subcutaneous or intramuscular administration of the drug needs doses that are 10–20 times more. It leads to accumulation of a drug into the central nervous system and occurrence of different side effects: vomiting, convulsions, activation of vagal centre resulting in cardiac arrest, etc. Therefore, lobeline and cytitonum are administered only intravenously in minimal doses.

An excitation of N_n-cholinergic receptors of sympathetic ganglia, adrenal medulla, carotid bodies, and posterior pituitary results in short-time elevation of blood pressure. It is necessary to remember that overdose of N-cholinomimetics results in blockage of correspondent receptors: effect of breathing stimulation disappears, and hypotension develops.

N-cholinomimetics are ineffective against the background of action of ganglionic blocking drugs.

Lobeline and cytitonum are used to restore breathing in patients poisoned by barbiturates, opioid analgesics, carbone monoxide, etc. Also, these drugs are used to restore breathing in cases of its inhibition due to operations, drowning, and traumas. About 0.2–0.5 ml of 1 % lobeline solution or 0.5 ml of cytitonum is slowly administered intravenously. If it is necessary, cytitonum may be administered repeatedly in 10–20 minutes.

It should be noticed that artificial ventilation is more reliable and effective than the use of respiratory analeptics.

Besides, N-cholinomimetics are used to stop smoking. The drugs are prescribed according to the therapeutic scheme with gradual dose reduction. The course of treatment lasts 20–25 days. The following drugs are used: tablets *"Tabex"* containing cytosine, and tablets *"Lobesil"* containing lobeline; anabasine in peroral or sublingual tablets, buccal plates, or chewing gum *"Gamibazin"*. Anabasine is an alkaloid contained in the tree tobacco.

Table 7 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Proserinum	Orally 0.01–0.015 g; subcutaneously 0.0005 g; in the eye: 1–2 drops	Tablets 0.015g; ampoules 1 ml of 0.05 % solution; 0.5 % ophthalmic solution
Galanthamini hydrobromidum	Subcutaneously 0.0025–0.005 g	Ampoules 1 ml of 0.1, 0.25, 0.5 or 1 % solution
Pilocarpini hydrochloridum	In the eye: 1–2 drops of ophthalmic solution or ophthalmic ointment	1 or 2 % ophthalmic solution in vials 5 or 10 ml; 1 or 2 % ophthalmic ointment
Aceclidinum	In the eye: 2–5 % ophthalmic solution (1–2 drops) or 3–5 % ophthalmic ointment; subcutaneously 0.002 g	2–5 % ophthalmic solution; 3 and 5 % ophthalmic ointment; ampoules 1 or 2 ml of 0.2 % solution
Carbacholinum	In the eye: 1–2 drops of 0.5–1 % ophthalmic solution	0.5 or 1 % ophthalmic solution in vials 5 or 10 ml
Dipiroximum	Subcutaneously, intramuscularly or intravenously 0.15–0.3 g	Ampoules 1 ml of 15 % solution
Alloximum	Intramuscularly 0.075 g dissolved in 1 ml of sterile water	Ampoules 0.075 g of powder for injection
Lobelini hydrochloridum	Intravenously slowly 0.005 g	Ampoules 1 ml of 1 % solution
Cytitonum	Intravenously slowly 0.5 ml	Ampoules 1 ml

Step 1. Tasks for Self-Control
Cholinomimetic Drugs

1. During operation the anaesthesiologist has overdosed tubocurarine chloride to a patient. Proserinum has been prescribed. What is the base of proserinum action in this case?

A. Blockade of adrenoceptors.

B. Increase of cholinesterase activity.

C. Blockade of presynaptic membrane.

D. Inhibition of cholinesterase activity.

E. Stimulation of M-cholinoceptors.

2. A patient is delivered into a hospital with complaints of dizziness, decrease of vision acuteness, nausea, hypersalivation, and abdominal cramps. The diagnosis is poisoning with organophosphorus compounds. What drugs should be included in the complex therapy?

A. Glucose and bemegride.

B. Atropine sulfate and dipyroxime.

C. Thiosulfate sodium and bemegride.

D. EDTA.

E. Naloxone and bemegride.

3. A patient with complaints of dry mouth and skin, vision disturbances, mydriasis, and tachycardia has been delivered into hospital. The doctor has put the diagnosis of poisoning with Belladonna's alkaloids. What drug should be prescribed?

A. Dipyroxime.

B. Aceclidine.

C. Pilocarpine.

D. Armine.

E. Neostigmine (proserinum).

4. Residual phenomena are observed in a child after poliomyelitis. What drug should be prescribed in this case?

A. Pyrroxane.

B. Pentamine (azamethonium).

C. Galantamine.

D. Dimecoline.

E. Atropine sulfate.

5. A victim treated the plants with insecticides without personal protective equipment. After some time, he developed the following symptoms: hypersalivation, sweating, diarrhea, miosis, and pain in the abdomen. The drug, which has caused this poisoning, is included to the group of:

A. Organic chloride compounds.

B. N-cholinomimetics.

C. Cuprum salts.

D. Nitrates.

E. Cholinesterase inhibitors.

6. After instilling eye drops the miosis and short-sightedness has developed in a patient with glaucoma. The intraocular pressure has decreased. What group of drugs can cause such effect?

A. Ganglioblockers.

B. M-cholinoblockers.

C. α-Adrenomimetics.

D. N-cholinomimetics.

E. M-cholinomimetics.

7. Paresis of intestine has developed in a patient after surgery. What drug from the group of cholinesterase inhibitors should be prescribed to this patient?

A. Acetylcholine.

B. Carbacholine.

C. Neostigmine (proserinum).

D. Aceclidine.

E. Pilocarpine.

8. A 5-year-old child has been delivered to emergency department with the following symptoms: marked psychomotor excitation, delirium, hallucinations, hoarse voice, dilatation of pupils, hyperemia of the skin, tachycardia, tachypnea. These symptoms were developed after the child had used the berries of Belladonna. What group of drugs should be prescribed for treatment of the child?

A. Cholinesterase regenerators.

B. N-cholinomimetics.

C. M-cholinomimetics.

D. Cholinesterase inhibitors.

E. N-cholinoblockers.

9. The disturbances of breathing had developed in a patient during operation with the use of peripheral myorelaxants. The administration of proserinum improves the patient's condition. What is such interaction of drugs called?

A. Antagonism.

B. Cumulation.

C. Synergism.

D. Incompatibility.

E. Tachyphylaxis.

10. A 4-year-old boy was delivered to a toxicological department with poisoning by berries of Belladonna. What drug should be prescribed to the boy in this condition?

A. Platyphyllin.

B. Aceclidine.

C. Lobeline.

D. Cytitonum.

E. Galantamine.

11. The peristaltic of intestine was not restored in a patient after resection of stomach. What drug should be prescribed to the patient for stimulation of GI-tract function?

A. Succinylcholine (dithylinum).

B. Platyphyllin.

C. Neostigmine (proserinum).

D. Cyclodol.

E. Atropine.

12. A patient with complaints of weakness and disturbances of gait came to the doctor. The doctor has diagnosed myasthenia and prescribed to the patient the injection of proserinum. What is the mechanism of proserinum action?

A. Inhibition of cholinesterase.

B. Activation of acetylcholine synthesis.

C. Direct stimulation of cholinoceptors.

D. Stimulation of metabolic processes.

E. Inhibition of brake processes.

13. A 40-year-old male was delivered to a toxicological department with poisoning by insecticides. What cholinesterase regenerator drug should be prescribed to the patient?

A. Atropine.

B. Platyphyllin.

C. Scopolamine.

D. Amizylum.

E. Dipyroxime.

14. What drug, which can cause miosis, will keep the action in an animal with denervation of smooth muscles of the eye?

A. Reserpine.

B. Galantamine.

C. Proserinum.

D. Pilocarpine.

E. Prazosin.

15. A female received injections of galantamine for restoration of CNS functions after the ischemic stroke. The condition of the patient has significantly improved. What is the mechanism of this drug action?

A. Blockade of monoamine oxidase.

B. Blockade of cholinesterase.

C. Blockade of cholinoceptors.

D. Blockade of catechol-ortho-methyltransferase.

E. Blockade of dopamine hydroxylase.

16. A 65-year-old male is accepted in a neurological department with the post-stroke syndrome. What drug should be prescribed for acceleration of this patient's recovery?

A. Aceclidine.

B. Galantamine hydrobromide.

C. Ipratropium bromide.

D. Dipyroxime.

E. Isonitrosine.

17. Drug *A* was prescribed to a patient with myasthenia and caused the improving of muscles activity. But several side effects had developed gradually: hypersalivation, sweating, diarrhea, nausea. What drug was used for treatment of the patient?

A. Armine.

B. Metamizole (analginum).

C. Strychnine.

D. Caffeine.

E. Neostigmine (proserinum).

18. A physician has prescribed eye drops with proserinum to a patient for decreasing intraocular pressure. What is the mechanism of proserinum action?

A. Blockade of phospholipase.

B. Blockade of cyclooxygenase.

C. Blockade of lipoxygenase.

D. Blockade of phosphodiesterase.

E. Blockade of cholinesterase.

19. The victim was delivered to an emergency department with complaints of dryness in the mouth, photophobia, and disturbances of vision. Hyperemia, dryness of skin, and tachycardia are observed. The diagnosis is the poisoning with alkaloids of Belladonna. What drug should be prescribed?

A. Dipyroxime.

B. Proserinum.

C. Diazepam.

D. Pilocarpine.

E. Armine.

20. The atony of intestine has developed in a patient on the 3rd day after the resection of the stomach. What drug should be used?

A. Proserinum.

B. Pirilenum.

C. Atropine sulfate.

D. Hexamethonium (benzohexonium).

E. "No-spa" (drotaverine).

21. A 2-year-old child has had a drink of eye drops from the first-aid set. The child has significant sweating and hypersalivation, difficult breathing, and cough. The pupils are narrowed, and bradycardia is observed. The peristaltic of intestine is increased. The blood pressure is low. What drug has caused poisoning?

A. Sulfacetamide (sulfacylum-sodium).

B. Propranolol (anaprilinum).

C. Pilocarpine hydrochloride.

D. Atropine.

E. Platyphyllin.

22. A patient was delivered to an emergency department with such symptoms: miosis, hypersalivation, sweating, vomiting, diarrhea, and spasm of bronchi. The diagnosis of poisoning with organophosphorus substances was ascertained. What drugs should be included in the complex therapy?

A. Panangin and unithiol.

B. Thiosulfate sodium and bemegride.

C. Nalorphine hydrochloride and bemegride.

D. Atropine sulfate and dipyroxime.

E. Glucose and bemegride.

23. Analeptic of reflective type from the H-cholinomimetics group was given to the patient for restoration of breathing after poisoning with carbon monoxide. What medicine was prescribed to the patient?

A. Atropine sulfate.

B. Lobeline hydrochloride.

C. Phenylephrine (mesatonum).

D. Adrenaline hydrochloride.

E. Pentaminum.

24. A 50-year-old male farm worker has been brought to the emergency room. He was found confused in the orchard and since then has remained unconscious. His heart rate is 45 and his blood pressure is 80/40 mm Hg. He is sweating and salivating profusely. Which of the following should be prescribed?

A. Pentaminum.

B. Proserinum.

C. Physostigmine.

D. Noradrenaline.

E. Atropine.

25. A child has residual phenomena after poliomyelitis. What drug is to be prescribed?

A. Pyroxanum.

B. Galantamine hydrobromide.

C. Pentaminum.

D. Dimecoline.

E. Atropine sulfate.

26. An injection of galantamine hydrobromide was made to a woman, 63-year-old, after the ischemic stroke. Condition of the patient has considerably improved. What is the mechanism of this medication effect?

A. Inhibition of monoamine oxidase.

B. Inhibition of cholinergic receptors.

C. Inhibition of catechol-o-methyltransferase.

D. Inhibition of dopamine-hydroxylase.

E. Inhibition of acetylcholinesterase.

27. It is necessary to prescribe a medication to a patient with glaucoma diagnosis. Which anticholinesterase drug (tertiary amine) isn't used in ophthalmologic practice due to its irritative influence on the eye conjunctiva?

A. Armine.

B. Galantamine hydrobromide.

C. Pyridostigmine bromide.

D. Aceclidine.

E. Proserinum.

28. A patient with myasthenia was prescribed a drug which improved muscle performance. But several defects have been revealed gradually: intensive salivation, transpiration, diarrhea, nausea. What drug was used for treatment?

A. Armine.

B. Analginum.

C. Strychnine nitrate.

D. Caffeine sodium benzoate.

E. Proserinum.

29. A 25-year-old man appeals to a neurologist with complaints of weakness in legs and gait disorder. The doctor diagnoses myasthenia and prescribes to the patient an injection of proserinum. What is the typical action of this drug?

A. Activation of acetylcholine synthesis.

B. Prevention of acetylcholine destruction.

C. Direct cholinomimetic.

D. Stimulation of metabolic processes.

E. Ganglion blocking.

30. A child poisoned with mushrooms, namely fly agarics, has been taken to a toxicological department. What drug should be primarily used for emergency?

A. Dipiroxime.

B. Papaverine hydrochloride.

C. Unithiol.

D. Sodium thiosulfate.

E. Atropine sulfate.

31. A child, 2-years-old, has drunk eye drops from the domestic first-aid kit. The child's condition is poor, accompanied by transpiration and salivation, asthmatic breathing, cough, sharply miotic pupils, muffled heart sounds, bradycardia, low arterial pressure, intensive intestinal peristalsis, diarrhea. What is the drug which has caused the poisoning?

A. Sulfacyl sodium.

B. Propranolol.

C. Pilocarpine hydrochloride.

D. Atropine sulfate.

E. Platyphyllin hydrotartrate.

32. A victim sprayed the plants with an insecticidal solution without personal protection equipment. After a while salivation, transpiration, tears secretion, pain in the stomach, and diarrhea began. Examination revealed miosis. What group does the substance, which has caused such symptoms, belong to?

A. Organic compounds of chlorine.

B. N-cholinomimetics.

C. Copper salt.

D. Organic compounds of phosphorus.

E. Nitrates.

33. Having used eye drops, a patient with glaucoma has developed miosis and myopia, intraocular pressure has decreased. What group of drugs causes such effect?

A. M-cholinomimetics.

B. Ganglionic blockers.

C. M-cholinergic blockers.

D. α-Adrenergic blockers.

E. N-cholinomimetics.

34. An 18-year-old unconscious patient was delivered to an urgent unit with the signs of dry skin and widened pupils. It is known, that the patient has poisoned with berries of Belladonna which contain M-cholinoblocker atropine. What drug should be prescribed to the patient?

A. Platyphyllin.

B. Proserinum.
C. Adrenaline.
D. Pilocarpine.
E. Propranolol (anaprilinum).

35. A victim with acute poisoning by fly-agaric was delivered to an urgent department. What drug should be prescribed to him?

A. Omeprazole.
B. Dithylinum.
C. Diazolinum.
D. Furacilinum.
E. Atropine sulfate.

36. The agent which decreases intraocular pressure is prescribed to a patient with glaucoma. Indicate this agent.

A. Proserinum.
B. Penicillin.
C. Noradrenaline.
D. Phenazepam.
E. Analginum.

37. Paralysis of bladder muscles has developed in a patient owing to surgery. What group of drugs should be prescribed to this patient?

A. Antianginal drugs.
B. Diuretics.
C. Antibiotics.
D. Adrenoblockers.
E. Cholinesterase inhibitors.

M-Cholinoblocking Drugs (Muscarinic Antagonists)

These agents selectively block M-cholinergic receptors and prevent the acethylcholine action. M-cholinoblocking drugs are classified as follows:

1. Alkaloids: *atropine, extract* and *tincture of Belladonna, scopolamine,* and *platyphyllin*.

2. Synthetic agents: *metacinium, ipratropium bromide* (*Atrovent*), *tiotropium bromide (Spiriva), pirenzepine* (*Gastrocepine*), *homatropine,* and *tropicamide*.

Natural muscarinic antagonists are used for millennia as medicines and cosmetics. For example, inhabitants of Ancient India used Mandrake root containing scopolamine for analgesia during operation.

Besides scopolamine, atropine (hyoscyamine) and platyphyllin are alkaloids of natural origin. Atropine is contained in the plant *Atropa belladonna* (deadly nightshade) and in *Datura Stramonium* (jimsonweed or thorn apple). Platyphyllin is alkaloid of plants of genus *Senecio*.

All drugs, except pirenzepine block all subfamilies of M-cholinoceptors (M_1, M_2, M_3, M_4, and M_5). Pirenzepine is selective M_1-cholinergic antagonist.

Ancestor of M-cholinergic antagonists is *atropine*. It is racemic mixture of *d*-hyoscyamine (dextrorotatory isomer) and *l*-hyoscyamine (laevorotatory isomer). The *l*-isomer of atropine is significantly more potent pharmacological agent than *d*-isomer. The peripheral effects predominantly occur due to the action of *l*-isomer. Effects of atropine in the central nervous system are the result of *d*-isomer action.

Atropine interacts with anionic site of M-cholinergic receptor. A very high distance between nitrogen atom and ester bond in atropine molecule interfere the binding of atropine to esterase site of receptor. Due to this, the interaction between acetylcholine and receptor becomes impossible. The affinity of atropine to M-cholinergic receptors is 1 000 times more than acetylcholine affinity. A molecule of atropine prevents the stimulation of 4 receptors by acetylcholine.

Therefore, the antagonism between atropine and acetylcholine has one-way character.

When low doses of atropine are administered, the short-term phase of stimulation of postsynaptic M-cholinergic receptors precedes the phase of their blockade. This short-term excitation develops owing to the blockade of the presynaptic M_2-cholinergic receptors that leads to the increase of acetylcholine release into the synaptic cleft. Thus, administration of a low dose of atropine often results in initial short-time bradycardia.

Atropine in therapeutic doses does not affect N-cholinoceptors. Their blockage is possible only due to the administration of high doses of atropine.

The following effects are observed after administration of therapeutic doses of atropine.

Cardiovascular system. The sinoatrial node is very sensitive to the action of M-cholinergic antagonists and atropine administration results in tachycardia. But, as mentioned above, the low dose of atropine can cause the initial bradycardia due to initial blockage of presynaptic M_2-cholinoceptors. The degree of tachycardia depends on the atropine dose and initial vagal tone. Children and elderly patients commonly have a naturally high heart rate; therefore, they do not have noticeable tachycardia as a result of taking muscarinic antagonists. Most marked tachycardia is observed in age group from 17 to 22 years.

Also, atropine significantly facilitates the conduction through atrioventricular node and reduces the PR interval of the ECG. Atropine improves coronary circulation, but it does not compensate the sharply increased oxygen demand of the heart.

Respiratory system. Administration of antimuscarinic agents causes the bronchodilation and reduces the secretion of bronchial glands owing to the blockage of M_3-cholinergic receptors. It is necessary to note, that M-cholinergic antagonists are more effective in bronchospasm that is caused by cholinesterase inhibitors or directly-acting M-cholinomimetics. In treatment of bronchial asthma, the therapeutic effect of antimuscarinic agents is less than effect of adrenomimetics.

M-cholinoblockering drugs are commonly used before the administration of inhalant anesthetics to reduce the accumulation of secretions in the trachea and the possibility of laryngospasm.

Gastrointestinal tract. The muscarinic antagonists exhibit the antispasmodic action upon the gastrointestinal tract. Both tone and motility of gastrointestinal tract are decreased. The gastric emptying time is prolonged, and intestinal transit time is lengthened. Therefore, atropine is contraindicated in patients with tendency to intestinal paresis and with paralytic ileus. M-cholinergic antagonists also decrease the tone of the gallbladder and sphincters of bile ducts. It results in the increase of bile discharge into intestine. Muscarinic antagonists significantly reduce the salivary secretion (dry mouth). Gastric secretion is decreased in less degree. Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol. M-cholinergic antagonists insignificantly reduce the pancreatic and intestinal secretions because these processes are mainly under hormonal control then under vagal influence.

Urogenital tract. M-cholinergic antagonists relax the smooth muscles of the urinary tract and bladder wall and slow voiding. This action is useful in the treatment of spastic conditions of urinary tract which can be induced by inflammation, urolithiasis, and surgery. But M-cholinergic antagonists can increase the urinary retention in patients with prostatic hyperplasia. Also, these drugs decrease the tone of uterus neck, but have no significant effect on the uterus.

Sweat glands. M-cholinergic antagonists suppress the sweating due to the blockage of M_3-cholinergic receptors of sweat glands receiving sympathetic cholinergic innervation. In adults, only large doses of atropine cause the increase of body temperature. But in infants and children even mean therapeutic doses may cause the so-called “atropine fever”.

Eye. The effects of M-cholinergic antagonists in the eye are opposite to effects of muscarinic agonists. Antimuscarinic drugs block the M-cholinergic receptors of the iris sphincter muscle and cause the mydriasis. The blockage of M-cholinergic receptors of ciliary muscle results in cycloplegia (paralysis of accommodation). Curvature of lens

is reduced, and eye cannot focus for near vision. Owing to mydriasis and cycloplegia, the outflow of the aqueous humor from the anterior chamber is worsened. It can provoke the elevation of intraocular pressure.

Central nervous system. The therapeutic doses of atropine exhibit insignificant stimulative effect in the central nervous system. High doses of atropine markedly stimulate the brain cortex and cause the motor and verbal agitation. Central effects of scopolamine significantly differ from the effects of atropine. Therapeutic doses of scopolamine produce the sedation, drowsiness, inhibition of extrapyramidal system, and affect the impulse transmission from the pyramidal passways to the motoneurons of spinal cord. Scopolamine reduces the tremor in patients with Parkinson's disease. Also, scopolamine prevents or eliminates the vestibular disturbances that developed after operation on the inner ear or in patients with kinetosis (motion sickness).

M-cholinoblockers differ in their degree of influence upon different inner organs. Atrovent, metacinium, and atropine cause most marked bronchodilation. Platyphyllin and scopolamine have less influence upon the tone of smooth muscles of bronchi. The antispasmodic action upon the smooth muscles of intestine, biliferous and urinary tracts is more marked in scopolamine, atropine, and metacinium than in platyphyllin. But, additionally to M-choliblocking action, platyphyllin has direct antispasmodic action. Also, platyphyllin blocks the ganglia and suppresses the vasomotor centre. The action of scopolamine upon the eye and glands' secretion is more potent than action of atropine. But duration of scopolamine's effects is less. Atropine has the longest effects upon the eye.

Metacinium is a synthetic mono-quaternary ammonium compound. Therefore, metacinium blocks peripheral M-cholinergic receptors only.

Ipratropium bromide is polar water-soluble synthetic agent used only as inhalations in patients with bronchial asthma.

Pirenzepine (Gastrozepin) is used in the treatment of peptic ulcers. This drug reduces gastric secretion of hydrochloric acid and decreases the smooth muscle spasm.

Synthetic agent homatropine is used only in ophthalmology.

The muscarinic antagonists with predominantly blocking action upon central M-cholinergic receptors (such as amizyl, benztropine mesylate) also are used in medical practice.

There are the following clinical applications of M-cholinolytics:

1. Atropine, metacinium, and scopolamine are used as preanesthetic agents (for so-called premedication). An administration of these agents prior to inhalant anesthetics decreases the accumulation of secretions in the trachea, reduces the possibility of laryngospasm, and prevents reflexive heart arrest.

2. M-blockering drugs (atropine, metacinium, ipratropium bromide, and tiotropium bromide) are used to treat bronchial asthma and chronic obstructive pulmonary disease (a condition that occurs with higher frequency in older patients, particularly chronic smokers).

3. Atropine and Belladonna-containing drugs are used to treat bradiarrhythmias owing to disturbances of atrioventricular conduction or in marked sinus bradycardia, including arising in initial stage of myocardial infarction.

4. Atropine, platyphyllin, metacinium, and Belladonna-containing drugs (such as tincture or extract of Belladonna) are used to treat spasms of smooth muscles of intestine, urinary and biliferous tracts. These agents are administered parenterally in the treatment for urinary or biliary colics. Antimuscarinic agents are also used in patients with diarrhea (especially in traveler's diarrhea).

5. Nowadays, non-selective M-cholinergic antagonists are rarely used in the treatment for hyperacid gastritis and ulcer disease of stomach and duodenum. Selective M_1-antagonist pirenzepine (orally or parenterally) is preferable in the therapy of these diseases.

6. Scopolamine and central antimuscarinic agents (such as amizyl and metamizyl) are used in Parkinson's disease.

7. Scopolamine is one of the oldest agents used to treat motion sickness. It can be administered in injections, taken orally (tablets

"Aeron"), or applied to the skin in the form of transdermal patch (*Transderm Scop*). The longest action is typical for a patch – from 48 to 72 hours.

8. M-cholinergic antagonists are widely used in ophthalmology with diagnostic and therapeutic aims: to examine eye fundus, select spectacles, to treat iridocyclitis and eye trauma. At inflammation of iris, the local use of M-cholinergic antagonists prevents the adhesion of the iris with lens capsule. The duration of eye effects of atropine lasts up to 7–10 days. Effects of scopolamine last from 3 to 7 days; eye effects of homatropine – 1–3 days; the action of tropicamide is about 6 hours.

9. Atropine is used in medical emergency for treatment of patients poisoned by cholinesterase inhibitors or muscarine.

10. Central M-cholinergic antagonists (metamizyl) reduce the intensity of brain oedema in patients with cranial traumas. The positive effect of metamizyl is observed also in children with motor disordes arising due to birth injures.

Treatment with M-blockering agents directed at the certain organ frequently induces undesirable effects in other organs. Thus, administration of antimuscarinic agents can result in dry mouth, cycloplegia, mydriasis, increase of intraocular pressure, tachycardia, obstipation, and urinary retention.

Muscarinic antagonists are contraindicated in patients with glaucoma, severe heart lesions (danger of myocardial exhaustion owing to tachycardia), prostatic hyperplasia, dismenorrhea, ulcerative gingivitis, and stomatitis.

Poisoning by M-cholinergic antagonists is occurred as a result of attempted suicide, inadvertent eating of Belladonna's berries by children, or due to attempts to induce hallucinations. The initial symptoms arise in 2–3 hours after poisoning and include the dry mouth, mydriasis, tachycardia, and hot and dry skin. After that, the central symptoms occur: motor and verbal agitation, hallucinations, seizures, and delirium. The body temperature is rising. It should be noticed that children, especially infants, are very sensitive to the hyperthermic effect of atropine.

The lethal dose of atropine for adults is 150–200 mg (but sometimes administration of over 400 mg has been followed by recovery). In children, 10–15 mg of administered atropine can result in the death.

Poisoning by atropine is mainly treated symptomatically: gastric lavage with absorbents, administration of saline laxative drugs, intravenous plasma-substitutive drugs, and temperature control with cooling blankets. Diazepam is used to cessate marked psychomotor agitation. β-adrenergic antagonists (propranolol) are used to reduce tachycardia. Parenteral administration of proserinum (neostigmine) partly relieves the peripheral effects of M-blockers. The prognosis is favorable if a child remains alive during 36–48 hours.

Table 8 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
1	2	3
Atropini sulfas	Orally 0.00025–0.0005 g 1–3 times a day; subcutaneously or intramuscularly 0.00025–0.0005 g 1–2 times a day; intravenously 0.00025–0.0005 g; in the eye: 1 % ointment or 1–2 drops of 0.5–1 % solution (once a day)	Tablets 0.0005 g; ampoules 1 ml of 0.1 % solution; 0.5 % or 1 % solution of eye drops; 1 % eye ointment
Extractum Belladonnae siccum	Orally 0.02–0.04 g 2–3 times a day; rectally 0.02–0.04 g 1–2 times a day	Powders for internal use; suppositories 0.02 or 0.04 g
Scopolamini hydrobromidum	Orally or subcutaneously 0.00025 g; in the eye: 1–2 drops of 0.25 % solution 1–2 times a day	Powders for internal use; ampoules 1 ml of 0.05 % solution; 0.25 % ophthalmic solution

Continuation of the table 8

1	2	3
Platyphyllini hydrotartras	Orally 0.003–0.005 g 2–3 times a day; subcutaneously 0.002–0.004 g 1–2 times a day; in the eye: 1–2 drops of 1–2 % solution	Tablets 0.005 g; ampoules 1 ml of 0.2 % solution; 1 % or 2 % solution of eye drops
Methacinum	Orally 0.002–0.004 g 2–3 times a day; subcutaneously, intramuscularly or intravenously 0.0005–0.001 g 1–2 times a day	Tablets 0.002 g; ampoules 1 ml of 0.1 % solution
Aeronum	Orally 1–2 tablets prior or during travel (for treatment or prevention of motion sickness)	Tablets containing scopolamine 0.0001 g of and 0.0004 g of hyoscyamine (10 tablets in packing)

Step 1. Tasks for Self-Control M-Cholinoblocking Drugs (Muscarinic Antagonists)

1. Laryngospasm and hypersalivation have developed in a patient after introduction of thiopental sodium for initial anaesthesia. The previous introduction of what drug can prevent the development of these side effects?

A. Epinephrine hydrochloride.
B. Proserinum.
C. Alloxime.
D. Pirroxane.
E. Atropine sulfate.

2. A patient was delivered to an emergency department with poisoning by mushrooms, among which fly-agaric has casually appeared. The injection of atropine sulfate was prescribed to the patient as well as the gastric lavage, active carbon, saline laxative

drugs, and infusion therapy. Name a type of interaction between the atropine and muscarine.

A. Physicochemical antagonism.

B. Direct functional one-way antagonism.

C. Indirect functional antagonism.

D. Intermediary antagonism.

E. Chemical antagonism.

3. Nausea, vomiting, diarrhea, and twitching of skeletal muscles developed in a patient with myasthenia after administration of proserinum. What drug can eliminate these symptoms?

A. Phenylephrine (mesatonum).

B. Physostigmine.

C. Atropine.

D. Pyridostigmine bromide.

E. Isoprenaline (isadrinum).

4. As a rule, the attacks of bronchial asthma develop in a patient at night, and are accompanied by bradycardia, spastic pain of intestine, and diarrhea. What group of drugs can eliminate these symptoms?

A. Sympatholytics.

B. N-cholinoblockers and blockers of H_2-histamine receptors.

C. M-cholinoblockers.

D. α-Adrenoblockers.

E. β-Adrenoblockers.

5. It is necessary to expand the pupils for examination of the eye fundus. Call the drug, which is used for this purpose in a clinic.

A. Acetylcholine.

B. Atropine.

C. Pilocarpine.

D. Mesatonum.

E. Adrenaline.

6. The drugs of this group are used to decrease salivary glands secretion, prevention of laryngospasm, nausea, and bradycardia. Call this group.

A. Cholinesterase regenerators.

B. Myorelaxants.

C. M-cholinomimetics.

D. Inhibitors of cholinesterase.

E. M-cholinoblockers.

7. Bronchospasm has developed in a worker owing to the careless use of organophosphorus substances. What broncholytic should be used in this situation?

A. Ephedrine.

B. Atropine.

C. Berotec (fenoterol).

D. Aminophylline (euphyllinum).

E. Adrenaline.

8. Atropine is used as antidote in case of poisoning with fly-agaric mushrooms. What is the mechanism of atropine action, which causes the elimination of toxic effects of muscarine?

A. Competition for the same receptors.

B. Enzymatic.

C. Physico-chemical.

D. Anti-enzymatic.

E. Metabolic.

9. A 48-year-old male was delivered to a urologic department with symptoms of renal colic. Choose a drug which is the most rational in this case.

A. Fentanyl.

B. Atropine.

C. Morphine.

D. Metamizole (analginum).

E. Trimeperidine (promedol).

10. The decrease of salivation and expansion of pupils are developed in an experimental animal after introduction of a drug *X*. After the following intravenous administration of acetylcholine, the heart rate has not changed. Call the drug *X*.

A. Atropine.

B. Salbutamol.

C. Adrenaline.

D. Propranolol (anaprilinum).

E. Proserinum.

11. A female with glaucoma asked the pharmacist with the request to give her out the eye drops with atropine sulfate. But the pharmacist has explained her that this drug is contraindicated to her. Why atropine is contraindicated at glaucoma?

A. It oppresses eye reflexes.

B. It causes the increase of intraocular pressure.

C. It causes the paralysis of accommodation.

D. It causes the expansion of pupils.

E. It reduces the acuteness of vision.

12. A patient was delivered to the hospital with the following symptoms: dizziness, thirst, impairment of swallowing, bad vision of near subjects. The patient has tachypnoea, dilated pupils, and excitement. The blood pressure is 110/70 mm Hg, heart rate is 110 per 1 minute. These symptoms testify the overdose of:

A. Caffeine.

B. Morphine.

C. Ephedrine.

D. Atropine.

E. Aminazine (chlorpromazine).

13. Mydriasis and paralysis of accommodation have developed in a patient after instilling into eyes the solution of a drug *X*. Call the group, to which the drug *X* is referred.

A. α-Adrenomimetics.

B. M-cholinomimetics.

C. Cholinesterase inhibitors.

D. β-Adrenomimetics.

E. M-cholinoblockers.

14. A patient, who receives the treatment concerning bronchial asthma, also suffers from glaucoma. The drugs of which group are not recommended to this patient for treatment of asthma?

A. Adrenoblockers.

B. Adrenomimetics.

C. M-cholinoblockers.

D. Miotropic spasmolytics.

E. Glucocorticoids.

15. Atropine sulfate was prescribed to a patient for interruption of intestine colic. What disease is the contraindication for administration of atropine?

A. Dizziness.

B. Glaucoma.

C. Bronchial asthma.

D. Node tachycardia.

E. Hypotension.

16. A 6-year-old child was delivered to a hospital with markedly expressed symptoms of psychomotor excitement, impairment of swallowing, and hoarse voice. The skin is dry and hot. The pupils are dilated. Tachycardia is observed. The doctor established, that the child had taken some berries of dark-violet colour. What substance is the cause of poisoning?

A. Metacinium.

B. Pirenzepine.

C. Pilocarpine.

D. Platyphyllin.

E. Atropine.

17. It is necessary to prescribe M-cholinoblocker for a patient who suffers from ulcer disease of stomach (with hyperacidic syndrome) and glaucoma. What drug may be prescribed to this patient?

A. Metacinium.

B. Homatropine.

C. Adiphenine (spasmolytinum).

D. Atropine.

E. Scopolamine.

18. The increase of heart rate, mydriasis, and significant dryness of mucous membranes have developed in a patient after introduction of atropine. What drug should be prescribed to the patient for reduction of these symptoms?

A. Strophanthin.

B. Metacinium.

C. Proserinum.

D. Salbutamol.

E. Ephedrine hydrochloride.

19. A 40-year-old male was delivered to the hospital with acute attack of hepatic colic, which is accompanied by sharp pain. What drug should be introduced first?

A. Morphine.

B. Codeine.

C. Metamizole (analginum).

D. Pentazocine.

E. Atropine.

20. A patient with complaints of dryness in the mouth, photophobia, and vision disorders was admitted to the reception-room. Skin is hyperemic and dry, pupils are dilated, tachycardia. Poisoning with Belladonna alkaloids was diagnosed at further examination. What drug should be prescribed?

A. Dipyroxime.

B. Proserinum.

C. Pilocarpine.

D. Armine.

E. Diazepam.

21. Pirenzepine was prescribed to a woman for stomach ulcer treatment. What pharmacological group can this medication be referred to?

A. Local anaesthetics.

B. Acetylcholinesterase reactivators.

C. β-Adrenergic blockers.

D. Selective α_1-adrenergic blockers.

E. Selective M_1-cholinergic antagonists.

22. A doctor has been appealed to by a man who was preliminary examined by an ophthalmologist. The patient complains of thirst and bad vision of close subjects. Objectively he demonstrates tachypnoea, mydriatic pupils, general excitation, garrulity, though the speech is obscure. Arterial pressure is 110/70, pulse is 110 per minute. The overdose of which drug can cause these symptoms?

A. Caffeine sodium benzoate.
B. Atropine sulfate.
C. Morphine hydrochloride.
D. Ephedrine hydrochloride.
E. Aminazine.

23. Sharp pain in the eye area of a patient has developed after the use of atropine in eye drops during examination of the eye fundus. From anamnesis it became clear that the patient suffered from the mild form of glaucoma. Why atropine is contraindicative at glaucoma?

A. Atropine oppresses eye reflexes.
B. Atropine causes paralysis of accommodation.
C. Atropine narrows pupils.
D. Atropine increases intraocular pressure.
E. Atropine affects vision.

24. The victim with acute poisoning by fly-agaric was delivered to an urgent department. What drug should be prescribed to him?

A. Atropine sulfate.
B. Omeprazole.
C. Dithylinum.
D. Diazolinum.
E. Furacilinum.

25. Proserinum has been administered to a patient suffering from myasthenia. After its administration the patient has got nausea, diarrhea, twitch of tongue and skeletal muscles. What drug would help to eliminate the intoxication?

A. Physostigmine.
B. Mesatonum.
C. Pyridostigmine bromide.
D. Isadrinum.
E. Atropine sulfate.

26. A patient with drug intoxication is presented with the dryness of oral mucous membrane and mydriatic pupils. Such action of this drug is associated with the following effect:

A. Blockage of adrenoceptors.
B. Blockage of muscarinergic receptors.
C. Stimulation of nicotinergic receptors.

D. Stimulation of adrenoceptors.
E. Stimulation of muscarinergic receptors.

N-Cholinoblocking Drugs

N-cholinoblockers are divided into two main groups depending on the subfamily of N-cholinergic receptors blocked by these agents: ganglionic blockers (ganglioplegic drugs) and peripheral myorelaxants.

Ganglionic Blockers (Ganglioplegic Drugs)

Ganglionic blocking agents interact and competitively block the N_n-cholinergic receptors of sympathetic and parasympathetic ganglia, adrenal medulla, and carotid bodies. The lipophilic agents penetrate through the blood-brain barrier and block the centrally located N_n-cholinoceptors.

The ganglionic blockers are classified depending on the duration of action:

1. Drugs with short action (duration of action is 15–25 minutes):

– *arfonade (trimethaphan)*;

– *hygronium (trepirium).*

2. Drugs with intermediate duration of action:

– *benzohexonium (hexamethonium)* (duration of action is 2–4 hours);

– *pentaminum (azamethonium)* (duration of action is 1–2 hours);

– *pachycarpine* (duration of action is 6–8 hours).

3. Drugs with long action (duration of action is 8–12 hours):

– *pirilenum (pempidine)*.

Only two drugs of this group, pachycarpine and pirilenum, have the tertiary atom of nitrogen in their molecules and can penetrate the brain. All other ganglionic blockers are quaternary ammonium compounds and have no central effects.

A blockade of both sympathetic and parasympathetic ganglia leads to condition that is called “pharmacological denervation” of

inner organs. In this situation, the initial neuronal control of the activity of inner organs is significantly decreased or lost.

Especially essential changes are observed in activity of the cardio-vascular system. The ganglionic blockers markedly decrease the blood pressure. The vessels extend, because the entering of vessel-narrowing reflexes through sympathetic ganglia is blocked by the drug. It should be noticed that the dilation of arterioles and small arteries is more expressed than dilation of the venules. The blood is accumulated in a lower part of the trunk. Blood-filling of a small circle of circulation and pressure in it are decreased. Both preload and afterload upon the left ventricle are decreased due to the reduction of blood venous return and peripheral vascular resistance. Ganglionic blockers have no direct depressive influence upon myocardium. The cardio-vascular reflexes, including pathological (for example, in myocardial infarction, surgical trauma), are blocked. In patients with hemorrhage, the inhibition of compensatory reflexes can cause the dangerous drop of blood pressure. The decrease of systolic blood pressure lower than 80–70 mm Hg leads to hypoxia of the brain and heart. The blockade of N_n-cholinoceptors of adrenal medulla results in the reduction of adrenaline secretion. It also promotes hypotension and weakening of compensatory vascular reflexes.

A blockade of both sympathetic and parasympathetic ganglia causes the decrease of gastrointestinal secretion and motility. This property of ganglionic blockers can be used in the treatment for ulcer disease of stomach and duodenum. But a possibility of dangerous hypotension significantly restricts their use for this purpose. On the other hand, during long-time treatment of hypertension by ganglionic blockers, the blockade of parasympathetic ganglia of intestine can lead to the serious constipations that poorly respond to the therapy.

Some ganglionic blockers (e. g., pachycarpine) stimulate the uterine contraction activity due to the blockade of inferior mesenteric ganglion and direct action upon uterus. Also, ganglionic blockers stimulate the posterior pituitary and sensitize the myometrium to action of oxytocin and folliculin. Therefore, pachycarpine may be used to stimulate the parturition.

The serious complication of ganglionic blockers is expressed hypotension. These drugs inhibit the vascular reflexes regulating the blood redistribution at changes of body position. It is a result of blockage of both sympathetic ganglia and adrenal medulla. Blood is accumulated in vessels of lower part of the body. An acute dropping of cerebral circulation owing to the change of body position (from horizontal to vertical) can result in orthostatic collapse. To prevent collapse, the patient should lay down for 2 hours after administration of a ganglionic blocker. Prolonged hypotension can result in serious complications, such as cerebral necrosis foci; myocardial infarction; coronary, cerebral, and retinal vascular thrombosis; and renal failure.

The symptoms of overdose of ganglionic blockers are rather characteristic: frequent thread-like pulse, low blood pressure, mydriatic pupils that do not react to the light, warm and dry skin, and dizziness.

The collapse requires urgent care directed to restoration of the blood pressure. It is significant, that under ganglionic blockade vascular smooth muscles retain the ability to react upon the vasoconstrictive agents acting lower than ganglia. Moreover, in this case, the sensitivity of vessel walls to such vasoconstrictors is increased. Therefore, in case of overdose of ganglionic blockers, adrenomimetic agent (noradrenaline, mesatonum, or ephedrine) is administered intravenously. If intravenous administration is impossible, mesatonum or ephedrine is administered intramuscularly every 1–1.5 hours until stabilization of blood pressure.

There are the following therapeutic indications for ganglionic blockers:

1. Controlled hypotension. The agents with short duration of action (arfonade and hygronium) are preferable for this purpose. Controlled hypotension is the temporally decrease of blood pressure (to 70–80 mmHg) which is widely used in surgical practice. Controlled hypotension together with elevation of the operated body area creates the favorable conditions for surgeon work and decreases the bleeding. Controlled hypotension is used during extensive and traumatic surgical operations on the brain, pelvic organs, vessels, etc.

Ganglion blocker is administered intravenously drop-by-drop monitoring the blood pressure.

2. Acute edema of the brain or lungs. Hygronium, arfonade, benzohexonium, or pentaminum are administered intravenously monitoring the blood pressure.

3. Urgent care for patients with hypertensive crisis (pentaminum or benzohexonium is administered intravenously or intramuscularly).

4. Treatment of severe forms of hypertensive disease. It should be noticed that presently ganglionic blockers are rarely used for this aim. Sometimes, pirilenum is prescribed for inpatients.

5. Treatment of obliterating endarteritis and Raynaud's disease.

6. Pharmacological management of ulcer disease of stomach and duodenum (but nowadays ganglionic blockers are not used almost for this aim).

7. Very seldom, pachycarpine is used to stimulate parturition.

Ganglionic blockers are contraindicated in patients with concomitant diseases when a significant decrease in blood pressure can provoke the dangerous complications: hypotension of different origin, ischemic stroke, coronary insufficiency, renal or hepatic function disorders, atherosclerosis, and glaucoma.

Peripheral Myorelaxants

Peripheral myorelaxants selectively block postsynaptic N_m-cholinergic receptors of skeletal muscles (including respiratory) that leads to muscular relaxation.

An ancestor of this group is the poison "curare" – a mixture of extracts from different kinds of South American plant *Strychnos*.

Skeletal muscles of a human body are characterized by different sensitivity to myorelaxant action. The majority of agents block, first and foremost, neuromuscular synapses of the face and neck; after that – extremities and trunk. The respiratory muscles are more resistant to myorelaxantaction. The last thing, paralysis of diaphragm occurs which leads to the stop of breathing.

The wide use of myorelaxants in surgical practice began in 1942, when Canadian anesthesiologists Griffith and Johnson proved the possibility of big surgical operations under the light anaesthesia on the background of myorelaxation caused by curare. Nowadays, the meaning of myorelaxants in anesthesiology is extremely great.

Chemically, all myorelaxants are quaternary ammonium compounds and do not penetrate through the blood-brain barrier.

Depending on the mechanism of action, myorelaxants are classified as follows:

1. Nondepolarizing myorelaxants (duration of action is 20–50 minutes):

– *tubocurarine*;
– *pipecuronium*;
– *pancuronium*;
– *alcuronium*;
– *atracurium*;
– *vecuronium.*

2. Depolarizing myorelaxants (duration of action is 5–10 minutes):

– *dithylinum* (*suxamethonium*).

3. Mixed-action myorelaxants:

– *dioxonium* (duration of action is 20–40 minutes).

Nondepolarizing Myorelaxants

These agents compete with acetylcholine for binding with N_m-cholinergic receptors and prevent the neurotransmitter action. Owing to this, the depolarization becomes impossible. The chemical structure of non-depolarizing myorelaxants significantly differs from the structure of acetylcholine. The large molecules of non-depolarizing agents relatively weakly bind to N_m-cholinergic receptors and do not penetrate inside of muscular fibers. The binding of these molecules with cholinergic receptors is reversible. When a concentration of acetylcholine in synapses is increased (e. g., in inhibition of cholinesterase by proserinum), the mediator displaces the

molecules of myorelaxant from receptors. This results in restoration of neuromuscular transmission.

Nondepolarizing myorelaxants act 20–50 minutes. A repeated administration of nondepolarizing myorelaxants prolongs the duration of a drug action due to cumulation. These agents are used at long-time surgical operations and in the treatment for tetanus. The administration of myorelaxants causes the complete relaxation of skeletal muscles that provides the favorable conditions for surgeon's work and prevents the motor reaction to the surgery trauma. Thus, myorelaxant administration allows to perform surgical operation under the light anaesthesia that allows to avoid the complications of deep narcosis.

Myorelaxant administration is especially indicated if the disturbances of breathing are very probable during operation (e. g., intrathoracic surgery). In this case, myorelaxants create the necessary conditions for artificial ventilation.

It should be noticed that the selectivity of competitive myorelaxants to N_m-cholinergic receptors is relative. At fast drug administration or at administration of a large dose, these agents can cause the temporary blockade of N_n-cholinergic receptors of parasympathetic and sympathetic ganglia, adrenal medulla, and chemoreceptors of vessels. It can cause the decrease of blood pressure. Also, tubocurarine and, to a lesser extent, atracurium, can produce hypotension due to systemic histamine release. Myorelaxants do not directly suppress the myocardium and practically do not influence the central nervous system. Non-depolarizing myorelaxants have no direct effect on bronchial smooth muscle, but tubocurarine and mivacurium can cause bronchoconstriction due to the stimulation of histamine release.

The action of non-depolarizing myorelaxants can be stopped by administration of proserinum (so-called "decurarisation"). For this purpose, 3–4 ml of 0.05 % proserinum solution is administered intravenously against the background of the preliminary intravenous administration of 0.5–1 ml of 0.1 % atropine solution. The previous blockade of M-cholinergic receptors by atropine prevents the side

effects of proserinum arising due to indirect stimulation of M-cholinoceptors.

The nondepolarizing myorelaxants are partly metabolized in the liver and excreted through the kidneys. Therefore, the duration of action of non-depolarizing agents depends on functional activity of these organs. The repeated administration of non-depolarizing myorelaxants can result in cumulation.

Presently, such nondepolarizing agent as *atracurium (Tracrium)* is widely used. Atracurium is partly transformed in inactive metabolites in the blood plasma. Therefore, its action does not depend on the liver and kidney condition. Atracurium does not cumulate in the human body. The action of the drug is stable and easily stopped by proserinum administration. Atracurium practically does not cause any side effects.

Depolarizing Myorelaxants

These agents are structurally like acetylcholine. The molecule of *dithylinum* (*succinylcholine*, *suxamethonium*) consists of two molecules of acetylcholine connected by ether binding. Dithylinum excites N_m-cholinergic receptors and causes the depolarization of postsynaptic membranes. This depolarization is observed as muscular fibrillation. Unlike acetylcholine, dithylinum is not hydrolyzed by acetylcholinesterase. Hydrolysis of dithylinum is carried out by butyrylcholinesterase. Due to the low speed of hydrolysis, the drug interaction with receptors lasts several minutes. This leads to the stable excitation of a cell membrane and its reaction upon nervous stimuli becomes impossible. Therefore, dithylinum-induced relaxation of skeletal muscles develops after the phase of muscular fibrillation.

The phase of depolarizing blockade caused by dithylinum lasts 3–10 minutes. If the duration of a surgical operation is longer, dithylinum is administered repeatedly. As a result of administration of large doses of relaxant (1 g of dithylinum and more) and in patients with myasthenia gravis, after a short restoration of nervous-muscular transmission, the development of the second phase of blockade is possible. The mechanism of this phase isn't completely known. This

second phase of blockade develops gradually, can last several hours and leads to the muscular weakness and hypoventilation in postsurgical period. Unlike depolarizing phase, this second phase is cessated by proserinum.

The depolarizing agents don't penetrate through the blood-brain barrier. Unlike non-depolarizing myorelaxants, depolarizing agents don't suppress neurotransmission through the vegetative ganglia. Moreover, sometimes administration of dithylinum can cause the short-term cholinomimetic effects.

Dithylinum can cause cardiac arrhythmias owing to the release of potassium from the skeletal muscles into the blood. Also, dithylinum can cause the temporary increase of intraoccular pressure. Muscle pain developed due to initial muscular fibrillation is a typical side effect of dithylinum.

There are the following indications for clinical use of skeletal muscle relaxants:

1. The relaxation of glottis, muscles of pharynx, and muscles of neck before the tracheal intubation (dithylinum).

2. The relaxation of skeletal muscles of a patient during surgical operations under the general anaesthesia. It is the main purpose of the use of non-depolarizing myorelaxants (tubocurarine, atracurium, etc.) and dithylinum (bolus or drop-by-drop intravenous administration).

3. Myorelaxants are administered to the patients with respiratory failure who need the artificial ventilation: patients poisoned by hypnotics, tranquilizers, or convulsive poisons (strychnine); patients with serious craniocerebral traumas, insults, brain edema, meningitis, hypoxic coma, etc. The drugs with long action are used for this purpose.

4. The elimination of convulsions in a patient with tetanus, when the administration of other anticonvulsive agents (such as diazepam) is ineffective. In severe cases, the myorelaxation of a patient is supported from 2–3 to 7–10 days.

5. The reposition of bone fragments and reduction of joint dislocations.

M- and N-cholinoblockers

The group of M- and N-cholinoblockers is represented by such drugs as *aprofene*, *spasmolytinum (diphenyltropine)*, and *fenpiverinium bromide*. These agents block both M- and N-cholinergic receptors. It should be noticed that the ability of these drugs to block M-cholinergic receptors is less than ability of M-cholinolytics, and N-cholinolytic activity is less than activity of ganglionic blockers. Additionally, M- and N-cholinergic antagonists have the moderate antispasmodic activity. The following effects of these agents are used practically: antispasmodic action, ability to decrease the gastric secretion, and ability to dilate the blood vessels.

The indications for use of M- and N-cholinergic antagonists are as follows:

1. Spasms of smooth muscles of inner organs: spastic colitis, pylorospasm, biliary and renal colics.

2. Ulcer disease of stomach and duodenum (drugs are used seldom).

3. The obliterating endarteritis, Raynaud's disease, spasm of coronary and cerebral vessels. At these diseases, the most effective drug is aprofene.

M- and N-cholinoblockers are taken orally 2–4 times a day. Aprofene is also administered subcutaneously and intramuscularly.

Fenpiverinium bromide is commonly used together with pitofenone hydrochloride (papaverine-like agent) and analginum (metamizole): co-formulations "*Baralginum*", "*Maxigan*", "*Spasmalgonum*", etc.

An administration of M- and N-cholinoblockers is accompanied by dizziness, headache, dryness of mouth, hypotension, vision disturbances and other side effects. These drugs are contraindicated in patients with glaucoma.

Table 9 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Benzohexonium	Orally 0.1–0.2 g 3–6 times a day; subcutaneously or intramuscularly 0.025 g 1–2 times a day	Tablets 0.1 g; ampoules 1 ml of 2.5 % solution
Pirilenum	Orally 0.0025–0.005 g 2–5 times a day	Tablets 0.005 g
Pentaminum	Intramuscularly 0.05–0.1 g 2–3 times a day; intravenously slowly 0.01–0.025 g (before the administration, a single dose is mixed with 20 ml of sterile isotonic sodium chloride solution or glucose solution)	Ampoules 1 or 2 ml of 5 % solution
Hygronium	Intravenously drop-by-drop 0.04–0.08 g (as 0.1 % solution)	Ampoules or vials containing 0.1 g of powder for injection
Tubocurarini chloridum	Intravenously 0.0004–0.0005 g/kg	Ampoules 1 ml of 1.5 % solution
Dithylinum	Intravenously 0.0015–0.002 g/kg	Ampoules 5 or 10 ml of 2 % solution

Step 1. Tasks for Self-Control N-Cholinoblocking Drugs

1. The breathing does not restore more than 30 minutes after introduction of suxamethonium (dithylinum) to a patient for performing a short operation. What is the aid for this patient?

A. Forced diuresis.

B. Hemodialysis.

C. Hemosorption.

D. Blood transfusion.

E. Peritoneal dialysis.

2. A patient with fracture of the bottom jaw was delivered to the hospital. The myorelaxant was introduced to him for performing an operation. The short-term twitching of face muscles was observed after the drug introduction. What drug was introduced to the patient?

A. Mellictinum.

B. Tubocurarine chloride.

C. Pipecuronium.

D. Diazepam.

E. Suxamethonium (dithylinum).

3. The symptoms of overdose of dithylinum have appeared in a patient during operation. What measure can decrease these symptoms?

A. N-cholinoblockers.

B. Introduction of cholinesterase inhibitors.

C. Blood transfusion.

D. Ganglion blockers.

E. M-cholinoblockers.

4. The stopping of breathing had developed in a 42-year-old woman after operation on a kidney with the use of dithylinum. Choose the drug which can restore the muscles tone.

A. Blood plasma.

B. Galantamine.

C. Proserinum.

D. Strychnine nitrate.

E. Caffeine.

5. The curare-like drugs (myorelaxants) are used in clinic for decreasing or stopping impulse transmission from motor nerve endings to muscular cells. What is the mechanism of action of these drugs?

A. Decrease of mediator releasing in a synaptic cleft.

B. Blockade of Ca^{2+} moving through channels of postsynaptic membrane.

C. Inhibition of Na^{+}, K^{+}-ATPase activity.

D. Inhibition of acetylcholinesterase.

E. Blockade of N-cholinoceptors of postsynaptic membrane.

6. The breathing of a patient is not restored after ending of operation with reposition of a fractured bone of the hip. What drug should be introduced to the patient for elimination of relaxation?

A. Aceclidine.

B. Platyphyllin.

C. Proserinum.

D. Cyclodol.

E. Atropine.

7. A patient with dislocation of a glenohumeral joint was delivered to a hospital. For relaxation of skeletal muscles, the doctor introduced dithylinum to him. In the norm this drug acts during 5–7 minutes. But in this patient the drug action lasted for 8 hours. What is probable cause of this phenomenon?

A. Potentiation of effect by another drug.

B. Decrease of microsomal enzymes activity.

C. Decrease of drug excretion.

D. Material cumulation.

E. Hereditary insufficiency of blood cholinesterase.

8. It is necessary to prescribe the myorelaxation short-acting drug to a patient for reposition of the fractured bone of the hip. Choose the drug.

A. Mellictinum.

B. Arduan.

C. Tubocurarine.

D. Suxamethonium (dithylinum).

E. Decametonium.

9. The operation with the use of tubocurarine was performed to a patient with abdominal wound. In the end of operation after restoration of breathing, the doctor has administered gentamycin to the patient. But unexpectedly the breathing stopped, and skeletal muscles relaxed. What effect is the base of this phenomenon?

A. Sensitization.

B. Potentiation.

C. Cumulation.

D. Tolerance.

E. Antagonism.

10. The relaxation of skeletal muscles and inhibition of breathing have lasted more than 2 hours in a patient in the result of introduction of dithylinum. Indicate the enzyme, insufficiency of which in plasma is the cause of this phenomenon.

A. Glutathione peroxidase.

B. Butyrylcholinesterase.

C. Catalase.

D. Acetylcholinesterase.

E. Glucose-6-phosphate dehydrogenase.

11. The introduction of dithylinum to a patient with dislocation of a glenohumeral joint has caused the apnea. The doctor introduced proserinum to the patient, but breathing is not restored. What substance should be introduced to this patient?

A. Atropine.

B. Galantamine.

C. Dipyroxime.

D. Isonitrosine.

E. Blood.

12. Myorelaxant was introduced to a patient for relaxation of skeletal muscles before repositioning of the bone fracture. This introduction caused the respiratory arrest. After the introduction of fresh blood, the breathing has restored. Call the myorelaxant, which was introduced to the patient.

A. Pancuronium.

B. Dithylinum.

C. Diplacinum.

D. Tubocurarine chloride.

E. Pipecuronium.

13. The signs of tubocurarine overdose have arisen in a patient after operation. What drug group should be introduced to the patient for elimination of overdose?

A. N-cholinoblockers.

B. Ganglion blockers.

C. Adrenomimetics.

D. Cholinesterase inhibitors.

E. M-cholinoblockers.

14. Dithylinum (Lystenon) was introduced for tracheal intubation. After the end of operation, the breathing did not restore. What enzyme insufficiency is the cause of this phenomenon?

A. K, Na-ANPase.

B. Butyrylcholinesterase.

C. Succinate dehydrogenase.

D. Carbonic anhydrase.

E. N-acetyltransferase.

15. Tubocurarine was introduced to a patient for operation of the stomach resection. What drug should be introduced for restoration of breathing?

A. Proserinum.

B. Benzohexonium.

C. Dithylinum.

D. Cytitonum.

E. Aethymizole.

16. A patient with a fracture of an average part of the femur with displacement was delivered to traumatologic department. For reposition of the bone, 10 ml of 2 % dithylinum solution was introduced intravenously to the patient. Due to this, the long apnea and myorelaxation have developed. What enzyme insufficiency is the cause of this phenomenon?

A. N-acetyltransferase.

B. Transferase.

C. Butyrylcholinesterase.

D. Glucose-6-phosphate dehydrogenase.

E. Methemoglobin reductase.

17. After a short-term operative intervention with the use of dithylinum, for over 30 minutes a patient was noticed to have respiratory depression, previous muscle tone didn’t restore. What assistance is necessary to render to the patient?

A. Peritoneal dialysis.

B. Blood or plasma transfusion.

C. Hemodialysis.

D. Hemosorption.

E. Forced diuresis.

18. Before an operative intervention a dithylinum solution was injected to a patient and intubation was performed. After the operative intervention self-breathing didn't restore. What enzyme insufficiency in the organism of the patient predetermines such prolonged effect of the muscle relaxant?

A. Na^+, K^+-ATP-ase.

B. Succinate dehydrogenase.

C. Carbonic anhydrase.

D. N-acetyltranspherase.

E. Pseudocholinesterase.

19. Tubocurarine chloride was applied to a patient under combined narcosis as a muscle relaxant while performing the resection of the stomach. What antagonist should be injected to the patient to restore spontaneous breathing?

A. Benzohexonium.

B. Dithylinum.

C. Cytitonum.

D. Proserinum.

E. Aethymizole.

20. To a patient with femoral bone fracture with the purpose of reduction of the tone of cross-striated muscles with reposition of bone fragments it is necessary to prescribe muscle relaxant of a short-term action. What drug is expedient for prescribing to the patient?

A. Mellictinum.

B. Dithylinum.

C. Arduan.

D. Tubocurarine chloride.

E. Pirilenum.

21. During an operative intervention with additional use of hygronium the patient's arterial pressure has sharply decreased. What groups of drugs can normalize arterial pressure in the given situation?

A. N-cholinomimetics.

B. β-Adrenergic blockers.

C. Ganglionic blockers.

D. M-cholinoblockers.

E. α-Adrenomimetics.

22. Symptoms of dithylinum overdose appeared during an operative intervention. What actions will be expedient to reduce the phenomenon of overdose?

A. Transfusion of blood or plasma.

B. Introduction of N-cholinergic antagonist.

C. Introduction of anticholinesterase drugs.

D. Introduction of ganglionic blockers.

E. Introduction of M-cholinergic antagonist.

23. For the abatement or termination of excitation transmission from the nervous ending to a muscular fiber the curare-like substances – muscle relaxants – are clinically used. What is the mechanism of action of this pharmacological group?

A. Reduction of mediator elimination into the synaptic cleft.

B. Blockade of calcium ions passing through the channels of the presynaptic membrane.

C. Inhibition of Na^+, K^+-pumps activity.

D. Depression of acetylcholinesterase.

E. Blockade of postsynaptic membrane N-cholinergic receptors of the myoneural junction.

24. A 45-year-old female is delivered to an urgent unit. It is necessary to perform trachea intubation. What drug should be used in this case?

A. Gentamycin.

B. Nitroglycerin.

C. Dithylinum.

D. Metronidazole.

E. Atropine sulfate.

25. A patient with a limb fracture must be administered depolarizing drug from the myorelaxant group for a short-time surgery. What drug is it?

A. Cytitonum.
B. Dithylinum.
C. Pentamine.
D. Tubocurarine chloride.
E. Atropine sulfate.

Adrenergic Drugs

The adrenergic drugs bind to adrenergic receptors that are in postsynaptic membrane of effector cells near the endings of postganglionic sympathetic neurons. Adrenergic receptors are also found in a presynaptic membrane of adrenergic nerve endings. Also, adrenergic receptors are in the central nervous system.

A mediator of adrenergic neurons is noradrenaline (norepinephrine). Adrenaline (epinephrine) is produced by cells of adrenal medulla and released directly in the blood. Thus, adrenaline is hormone. Sometimes, dopamine plays the mediator role in adrenergic neurons. These three catecholamines are similar not only by chemical structure, but also by pharmacological effects.

Neurotransmission in adrenergic synapses involves five steps: the synthesis of norepinephrine, its storage, release, binding to correspondent receptors, and removal from the synaptic cleft.

A starting material for catecholamine synthesis is tyrosine. Tyrosine is transported into the axoplasm of the adrenergic neuron and hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. DOPA is decarboxylated to dopamine. Dopamine is transported into synaptic vesicles where it is hydroxylated to norepinephrine. In the adrenal medulla, norepinephrine is mainly transformed to epinephrine that is stored in chromaffin cells. Due to stimulation, adrenal medulla releases about 85 % of epinephrine and 15 % of norepinephrine in the blood.

In adrenergic synapses, about 80 % of synthesized norepinephrine is deposited in vesicles by means of binding with specific protein and ATP. Certain amount of noradrenaline persists as a cytoplasmic pool that is fastly released at the action of nervous stimuli.

Released norepinephrine diffuses across the synaptic space and binds to either postsynaptic receptors on the effector cell or presynaptic receptors on the nerve ending. The stimulation of adrenergic receptors by noradrenaline activates the formation of intracellurar second messengers that changes the cell activity.

Released noradrenaline may diffuse out of the synapse; undergoes metabolism by catechol O-methyltransferase (COMT) in the synaptic space; or undergoes reuptake by the neuronal endings with the following deposition in the vesicles. Part of norepinephrine is oxidized by monoamine oxidase (MAO) present in neuronal mitochondria. COMT is a cytoplasmic enzyme of effector cells that catalyzes O-methylation of catecholamines.

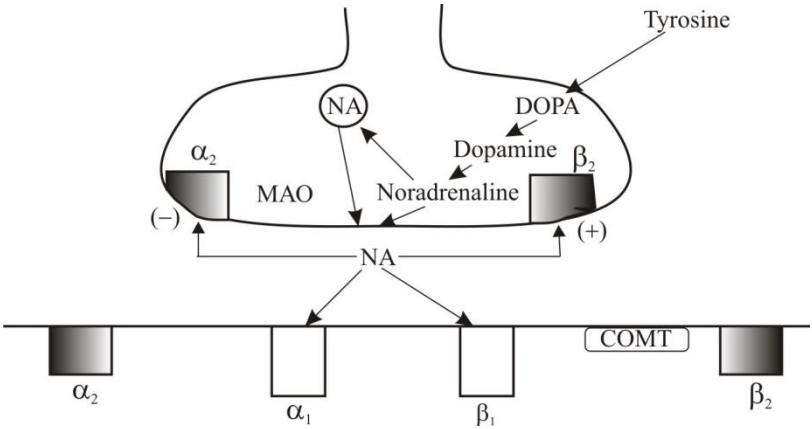

Figure 7 – The structure of adrenergic synapse

Adrenergic receptors are divided into α- and β-adrenoceptors.

α-Adrenoceptors are divided into α_1- and α_2-adrenoceptors. In turn, α_1-adrenoceptors are divided into α_{1A}, α_{1B}, and α_{1D}-receptors; and α_2-adrenoceptors are divided into α_{2A}, α_{2B}, and α_{2C}-receptors. These subtypes are located heterogeneously within the body. For

example, the prostate is rich in α_{1A}-receptors regulating contraction of smooth muscles of this organ. Whereas vascular smooth muscles contain mainly α_{1B}-receptors stimulating contraction of the vasculature. α_1-Adrenoceptors are located on a postsynaptic membrane of the effector organs within the synapse. α_2-Adrenergic receptors are located both on presynaptic and on postsynaptic membranes. It should be noticed that postsynaptic α_2-adrenergic receptors are located outside of the synapse. In vessels, they are in the inner layer that is not innervated. Obviously, these receptors are mainly activated by adrenaline circulating in the blood. α_1-Adrenoceptors are mainly activated by noradrenaline. The stimulation of presynaptic α_2-adrenoceptors leads to the reduction of the noradrenaline release (so-called negative feedback).

The excitation of all types of α_1-adrenoceptors leads (through G_q-proteins) to activation of phospholipase C and elevation of intracellular level of inositol triphosphate and diacylglycerol that promotes output of calcium from the intracellular depot and activation of corresponding protein kinases with the following contraction of smooth muscles.

The excitation of α_2-adrenoceptors results in the decrease of adenylyl cyclase activity (through G_i-proteins) and reduction of intracellular cAMP level. It leads to inhibition of activity of cAMP-dependent protein kinases. It is possible, that some effects of excitation of α_2-receptors (e. g., deceleration of mediator release from presynaptic endings) develop due to the activation of potassium channels with the following potassium outflow, hyperpolarization of membrane, and decrease of activity of calcium channels.

Depending on the affinity for adrenergic agonists and antagonists, β-adrenoceptors are divided into β_1-, β_2- and β_3-adrenoceptors. β_1-adrenergic receptors are located on a postsynaptic membrane within the synapses. β_2-adrenoceptors are located both on postsynaptic and on presynaptic membranes. Moreover, postsynaptic β_2-adrenergic receptors are located outside of the synapses and excited mainly by adrenaline circulating in the blood. Presynaptic β_2-adrenoceptors

regulate the positive feedback: their excitation increases the noradrenaline release into synaptic cleft.

The recently opened β_3-adrenoceptors are in the fat tissue, in the smooth muscles of gastrointestinal tract and gallbladder, and in the heart. β_3-Adrenoceptors are innervated by adrenergic nerves and are more sensitive to norepinephrine than to epinephrine. As a rule, this subfamily of β-adrenoceptors is activated by higher concentrations of catecholamines than the subfamilies of β_1- and β_2-adrenoceptors. Stimulation of β_3-adrenoceptors in adipose tissue activates lipolysis and thermogenesis. Activation of β_3-adrenoceptors in the heart leads to a decrease in the ventricular contractility. The function of β_3-adrenoceptors in smooth muscles is unclear.

β_1-Adrenoceptors have approximately equal affinity for epinephrine and norepinephrine, whereas β_2-adrenoceptors have a significantly higher affinity to epinephrine. β-Adrenoreceptors activate the adenylyl cyclase that leads to the elevation of cAMP level in the cell. It is accompanied by activation of cAMP-dependent protein kinases and changes of metabolism and functional activity of the cells. Thus, activation of β_1-adrenoceptors in the heart promotes the calcium entrance into the cardiomyocites and activates all functions of the heart. Activation of β_2-adrenoceptors in the smooth muscles causes their relaxation.

As mentioned above, inner organs and tissues are characterized by unequal density of different types and subtypes of adrenergic receptors. Thus, vasculature of skeletal muscles contains both α_1- and β_2-adrenoceptors, but the density of β_2-adrenoceptors is significantly higher. The heart contains predominantly β_1-adrenoceptors. The vasculature of skin and abdominal viscera contains predominantly α_1-adrenergic receptors. The smooth muscles of bronchi contain mainly β_2-adrenoceptors. The gastrointestinal tract contains both α- and β-adrenoceptors.

Table 10 – Predominant localization and effects of excitation of adrenergic receptors

Inner organ or tissue (predominant type of adrenergic receptors)	Effect of stimulation of adrenergic receptors
Medula oblongata (α_2)	Reduction of blood pressure and heart rate
Heart: sinus node, atrioventricular node, and cardiomyocytes of atria and ventricles (β_1)	Positive chronotropic action (accelerated heart rate). Positive dromotropic action (increased conductibility). Increase of contractility of atria and ventricles
Blood vessels: – skin and mucosa, abdominal viscera, renal (α); – skeletal muscles, lungs, brain, liver, coronary (β_2)	Constriction. Dilation
Bronchial muscles (β_2)	Relaxation
Gastrointestinal tract: – smooth muscles (α_2; β_2); – sphincters (α)	 Decreased motility and tone of gastrointestinal tract. Contraction
Pancreas (α_2; β_2)	Inhibiting of insulin release (α_2); stimulation of insulin release (β_2)
Sex organ, male (α)	Ejaculation
Bladder: – trigone (α); – detrusor (β)	 Contraction. Relaxation
Radial muscle of iris (α_1)	Contraction (mydriasis)
Epithelium of ciliary body of eye (β_1)	Increase of aqueous humour secretion
Salivary glands (α)	Thick, viscous secretion
Adipocytes (α_2; β_3)	Inhibition of lipolysis (α_2); stimulation of lipolysis (β_3)
Liver (α_1 and β_2)	Activation of glycogenolysis and gluconeogenesis; inhibition of glycogen synthase
Uterus (α_1; β_2)	Stimulation of uterine contraction (α_1); inhibition of uterine contraction (β_2)
Platelet (α_2)	Stimulation of platelet aggregation

Adrenergic drugs are divided into 2 groups: drugs which excite or lead to excitement of adrenoceptors (adrenomimetic drugs or adrenergic agonists) and drugs which block or diminish the excitement of adrenoceptors (antiadrenergic drugs or adrenergic antagonists).

I. Adrenergic agonists.

1. Adrenomimetic drugs of direct action.

1.1. α- and β-adrenomimetics: *noradrenaline (norepinephrine)* and *adrenaline (epinephrine)*.

1.2. α-Adrenomimetics:

– α_1-adrenomimetics: *phenylephrine (mesatonum)* and *midodrine*;

– α_2-adrenomimetics: *naphazoline (naphthyzinum, Sanorin), xylometazoline (halazolinum),* and *oxymetazoline.*

1.3. β-adrenomimetics:

– nonselective β-adrenomimetics: *isoprenaline (isadrinum)* and *orciprenaline*;

– selective β_1-adrenomimetics: *dobutamine (Dobutrex, Inotrex)*;

– selective β_2-adrenomimetics: *salbutamol (Ventolin), fenoterol (Partusisten, Berotec), terbutaline (Bricanyl),* and *formoterol.*

2. Sympathomimetics or α- and β-adrenomimetics of indirect action: *ephedrine* and *phenamine.*

II. Antiadrenergic drugs (adrenergic antagonists).

1. Adrenoblockers.

1.1. α, β-adrenoblockers: *labetalol, proxodolol,* and *carvedilol*.

1.2. α-adrenoblockers:

– $\alpha_{1,2}$-adrenoblockers: *phentolamine (regitine), pirroxane,* and *tropaphenum;*

– α_1-adrenoblockers: *prazosin (minipress), terazosin,* and *doxazosin (cardura);*

1.3. β-adrenoblockers:

– $\beta_{1,2}$-adrenoblockers: *propranolol (anaprilinum), nadolol, sotalol, oxprenolol,* and *pindolol;*

– β_1-adrenoblockers: *metoprolol, talinolol, atenolol, nebivolol,* and *acebutalol.*

2. Sympatholytics: *reserpine, guanethidine (octadinum),* and *bretylium tosilate (ornidum).*

α- and β-Adrenomimetics of Direct Action

This group includes *adrenaline* (*epinephrine*) and *noradrenaline* (*norepinephrine*).

Adrenaline (epinephrine)

Epinephrine directly interacts with both α- and β-adrenoceptors, but when a drug is given in therapeutic doses, the β-adrenoceptors are more sensitive to adrenaline. Depending on the degree of sensitivity to adrenaline, adrenoceptors are in the following sequence: β_2, β_1, α_2, and α_1.

Adrenaline exhibits the most expressive influence upon the cardio-vascular system. An excitation of β_1-receptors of the heart is accompanied by the following effects:

1. Tachycardia. It is a result of excitation of β_1-receptors of sinoatrial node that leads to the increased automatism.

2. Facilitation of atrioventricular conduction arises due to excitation of β_1-receptors of atrioventricular node.

3. Increase of myocardium contractility. The main mechanism of this effect is associated with adrenaline influence upon metabolism of carbohydrates, lipids, and calcium ions in the myocardium. Thus, adrenaline, through β_1-adrenergic receptors coupled with G_s-proteins, stimulates adenylyl cyclase and promotes cAMP synthesis in cardiomyocytes. It leads to activation of lipase (hydrolysis of lipids), phosphorylase (hydrolysis of glucogen), and promotes the elevation of intracellular concentration of calcium ions. It leads to the increase of stroke volume of the heart and cardiac output. But, increased metabolism of lipids and glycogen results in elevation of oxygen consumption by myocardium that can provoke the hypoxia of cardiac muscle in patients with pathological changes in coronary vessels. At disturbances of metabolism, the exhaustion of myocardium with the following heart failure develops. Therefore, epinephrine is not used in

the treatment of heart failure. Vice versa, epinephrine is contraindicated at diseases of the heart and coronary vessels.

There is evidence, that heart can selectively absorb epinephrine from the blood. In the heart, epinephrine binds with proteins that protect it from degradation. An increase of sympathetic tone (psychical and emotional excitation) leads to the release of this epinephrine that adversely affects metabolism in the myocardium. This fact has high meaning in the development of myocardial infarction.

The influence of epinephrine upon vascular system is complex. Epinephrine constricts arterioles in the skin, mucous membranes, and viscera owing to the excitation of α_1- and α_2-adrenoceptors. Renal blood flow is also decreased. But excitation of β_2-adrenergic receptors by epinephrine causes the vasodilation in the liver and in the skeletal muscles.

At low doses of epinephrine, excitation of β-adrenergic receptors with vasodilatation predominates, whereas high doses of epinephrine initially influence α-adrenergic receptors with the following vasoconstriction. At the average therapeutic doses of epinephrine, the summary effect is the increase of systolic blood pressure and the moderate reduction of diastolic blood pressure. Depending on an administered dose, the average blood pressure increases, decreases or remains without changes.

Adrenaline is unsuitable for treating the acute hypotension due to its negative influence upon the heart, weak influence upon diastolic blood pressure, and disorders of blood supply in some tissues and organs. As pressor agent, adrenaline may be used only in exceptional cases if other drugs increasing blood pressure are absent. An ability of adrenaline to constrict blood vessels is used by anaesthesiologists. Adrenaline is added to solutions of local anaesthetics. Such combination slows down the absorption of local anesthetic into the blood, prolongs the anaesthesia, decreases the toxicity of local anaesthetic, and decreases the bleeding from operative area.

Adrenaline stimulates the spleen contraction owing to excitation of α-adrenergic receptors.

Epinephrine increases the tone of gastrointestinal sphincters and slows down peristaltics of stomach and intestine. These effects do not have practical meaning.

Adrenaline causes bronchodilation due to excitation of β_2-adrenergic receptors of bronchial smooth muscles. Broncholytic action of adrenaline is higher than the same effect of atropine-like drugs. Adrenaline relieves all known allergic-induced bronchoconstriction (including anaphylactic shock) and acute attacks of bronchial asthma.

The radial muscle of the iris (*m. dilatator pupillae*) contains α_1-adrenoceptors. Epinephrine causes dilation of the pupil (mydriasis) by contracting the radial muscle. This effect is not accompanied by elevation of intraocular pressure because adrenaline causes the local vasoconstriction that reduces the production of aqueous humour. Thereby, 2 % adrenaline solution is sometimes used to treat glaucoma.

Uterine muscle contains both α- and β_2-adrenoceptors, excitation of which respectively causes either contraction or relaxation of the uterus. This adrenaline's effect depends on the endocrine balance. Stimulation of β_2-receptors is predominant during the last stage of pregnancy and during parturition; therefore, epinephrine relaxes the uterine muscle.

The detrusor muscle of the bladder body contains β_2-adrenoceptors and adrenaline relaxes it. On the other hand, the trigone and sphincter of bladder, containing α_1-adrenergic receptors, are contracted by epinephrine. This action inhibits the voiding.

Therapeutic doses of epinephrine mildly stimulate the central nervous system, excitate the centre of thermoregulation, and stimulate the secretion of adrenal cortex.

Adrenaline increases the glucagon release, stimulates glycogenolysis, and decreases the insulin release that leads to hyperglycemia. Excitation of β_3-adrenoceptors by epinephrine results in stimulation of lipolysis. The levels of free fatty acids, glucose, and lactic acid in the blood are increased.

Excitation of β_3-adrenoceptors located in the membranes of the mast cells (labrocytes) leads to a decrease of histamine release from these cells.

Epinephrine increases the working capacity of the skeletal muscles, especially on the background of the fatigue. The drug reduces the influence of kurare-like agents upon skeletal muscles. These effects are associated with the sensitization of skeletal muscles to acetylcholine. Besides, an increased carbohydrate metabolism in skeletal muscles, improved blood circulation, acceleration of carbohydrate metabolism and synthesis of ATP are also important.

Epinephrine has a rapid onset but short duration of action because COMT and MAO rapidly metabolize the drug. At subcutaneous administration, the duration of epinephrine action is about 30 minutes.

Epinephrine is widely used in urgent care. The drug is used to treat allergic reactions of immediate type: urticaria, angioneurotic edema, serum sickness. Epinephrine is the drug of choice to treat anaphylactic shock.

To treat the acute bronchoconstriction, epinephrine is administered intramuscularly or subcutaneously.

As mentioned above, 2 % epinephrine solution is used topically to reduce intraocular pressure in patients with open-angle glaucoma or for mydriasis.

Weak solutions of epinephrine are used topically to stop capillary bleeding (e. g., nosebleed). Epinephrine is added to local anaesthetic solutions (most commonly one part of epinephrine to 100 000 or 200 000 parts of anaesthetic solution).

The drug is used to treat hypoglycemic coma caused by insulin overdose.

Adrenaline is used in the treatment for cardiac arrhythmias associated with conductivity disturbances.

Epinephrine is administered intracardialy in the case of cardiac arrest. In this case, 0.3–0.5 ml of 0.1 % adrenaline solution is mixed with 10 ml of solution of sodium chloride or glucose and administered into the cavity of the left ventricle. Right after adrenaline administration, heart massage is performed.

Very seldom, adrenaline is used to elevate the low blood pressure.

Side effects of epinephrine are anxiety, headache, tremor, cerebral hemorrhage, cardiac arrhythmias, etc.

Norepinephrine (noradrenaline)

Noradrenaline directly stimulates α_1-, α_2-, and β_1- types of adrenergic receptors. It is necessary to notice that α-adrenergic receptors are more sensitive to noradrenaline.

The main effect of norepinephrine is the expressed but short-time increase of peripheral vascular resistance. Both systolic and diastolic blood pressure increases. Stimulation of baroreceptors due to hypertension induces the reflex increase of vagal activity that leads to bradycardia. But this reflex does not eliminate the positive inotropic effect of the norepinephrine. As a result, the cardiac output is practically not changed or even reduced, and stroke volume is increased.

It should be noticed that preliminary administration of atropine prevents the reflex bradycardia and in this case administration of noradrenaline results in tachycardia.

Noradrenaline acts several minutes because COMT and MAO rapidly inactivate it. Subcutaneously administered noradrenaline causes the local vascular spasm and, therefore, it is badly absorbed and can cause tissue necrosis. Therefore, subcutaneous or intramuscular norepinephrine administration is not permissible. Norepinephrine is administered intravenously drop-by-drop (to that end, 2–4 ml of noradrenaline solution is diluted in 1 litre of 5 % glucose solution).

Norepinephrine is used to combat acute hypotension (e. g., hypotension arising at the spinal anaesthesia, operations, traumas). But norepinephrine is not used in cases of hypotension developed due to most types of shock (e. g., hemorrhagic and cardiogenic shock which are accompanied by hypovolemia). In cases of shock, marked sympathetic activity is already present, and perfusion of organs, such as kidneys, may be worsened due to norepinephrine administration. In this case, α-adrenoblockers are administered after compensation of hypovolemia.

The side-effects of norepinephrine develop seldom and include the reflexive sinus bradycardia, respiratory disturbances, headache, and tissue necrosis in the site of norepinephrine injection.

Sympathomimetics

Sympathomimetics or indirectly-acting adrenomimetics include *ephedrine* and *phenamine.*

Mechanism of sympathomimetic action is associated with the following:

– these drugs induce release of the mobile pool of noradrenaline into the synaptic cleft;

– sympathomimetics slow down the mediator reuptake by the nervous endings;

– sympathomimetics decrease the MAO activity;

– these drugs are weak direct agonists of postsynaptic α- and β-adrenergic receptors.

A repeated administration of sympathomimetics with a short-time interval (10–30 min) leads to the fast weakening of their effects (so-called tahyphylaxis). It is associated with the decrease of norepinephrine storage in vesicles.

Ephedrine is alkaloid of the plant *Ephedra*. The drug has a long duration of action. The main effects of ephedrine are like those of epinephrine, but less apparent. Ephedrine increases the blood pressure, accelerates the heart rate, produces bronchodilation, inhibits the intestinal motility, and causes mydriasis. The drug penetrates the central nervous system and produces its stimulation. Ephedrine increases alertness, decreases fatigue, and prevents sleep. Also, ephedrine increases the tone of skeletal muscles and causes hyperglycemia.

Ephedrine is used in bronchial asthma treatment both to prevent asthma attacks (powders, tablets, and rectal suppositories) and to stop them (subcutaneous or intravenous injections). To treat arterial hypotension, ephedrine is administered subcutaneously, intramuscularly, intravenously, or taken orally. In cases of intramuscular administration, the blood pressure increases during 40–

60 minutes. Ephedrine is used topically to treat rhinitis and synusitis. The drug is used in the treatment for myasthenia gravis. Central stimulative effects of ephedrine are used to treat narcolepsy and poisoning by hypnotic drugs. The drug ability to improve the atrioventricular conduction is used in the treatment for atrioventricular blockage. Ophthalmic drops with ephedrine are used for mydriasis.

α-Adrenomimetics

α-Adrenomimetics are the drugs which selectively stimulate α-adrenergic receptors. This group includes α_1-adrenomimetics *mesatonum (phenylephrine)* and *midodrine* and α_2-adrenomimetics *naphthyzinum (naphazoline)* and *halazolinum (xylometazoline).*

Mesatonum stimulates α_1-adrenoceptors of the postsynaptic membranes. It is a synthetic adrenergic drug that is less potent than noradrenaline but acts longer (40–60 minutes). Mesatonum is administered subcutaneously, intramuscularly, intravenously, and taken orally. Drug is vasoconstrictor that raises both systolic and diastolic blood pressure. Mesatonum does not directly influence the heart but induces reflex bradycardia owing to the stimulation of baroreceptors in aortic arch and the following activation of nervus vagus. Mesatonum is often used topically on the nasal mucous membranes at rhinits and in ophthalmic solutions for mydriasis and at open-angle glaucoma. It is used to treat arterial hypotension and for prolongation of local anesthetics' action. Besides, mesatonum is used in the treatment for supraventricular tachycardia. It is also used to treat hypotension during halothane anaesthesia. Large doses of mesatonum can cause hypertensive headache.

Midodrine is used to treat hypotension and urinary incontinence (involuntary urination due to impaired bladder sphincter function). The drug is taken orally and administered intravenously.

Naphthyzinum and *halazolinum* selectively stimulate α_2-adrenergic receptors. Both drugs have longer vasoconstrictive effect than mesatonum. These drugs are used locally as nasal

decongestant in symptomatic treatment for rhinitis. The drugs cause local irritative effect.

β-Adrenomimetics

β-Adrenomimetics are drugs which directly stimulate β-adrenergic receptors. β-Adrenomimetics are classified as follows:

– nonselective β-adrenomimetics: *isadrinum (isoprenaline)* and *orciprenaline*;

– selective β_1-adrenomimetics: *dobutamine (dobutrex, inotrex)*;

– selective β_2-adrenomimetics: *salbutamol, fenoterol (Partusisten), terbutaline,* and *formoterol.*

Isadrinum stimulates β_1-, β_2-, and β_3-adrenergic receptors and acts upon the heart, smooth muscles, and metabolism. Stimulation of β_1-adrenoceptors increases the heart rate, myocardial contractility, excitability, automatism and conduction. Cardiac output is increased. Isadrinum increases systolic pressure but lowers diastolic pressure due to the stimulation of β_2-adrenergic receptors of blood vessels and the following vasodilation.

Stimulation of β_2-adrenoceptors of smooth muscles results in bronchodilation and reduction of the uterine tone. Isadrinum also stimulates glycogenolisis, lipolysis and gluconeogenesis. Isadrinum is used to eliminate the acute attacks of bronchial asthma. Duration of its bronchodilating effect is about 1 hour. The drug is also used in the treatment for atrioventricular blockade.

The side-effects of isadrinum are tachycardia, tremor, and headache. Isadrinum is contraindicated in ischemic heart disease, thyrotoxicosis, artherial hypertension, and diabetes mellitus.

β_2-adrenomimetics (*salbutamol, fenoterol, terbutaline, formoterol*) selectively stimulate β_2-adrenoceptors that results in bronchodilation. Also, these drugs decrease the uterine tone and weaken the partirition hyperactivity. This effect is called tocolytic action. Selective β_2-adrenomimetics are used to treat bronchial asthma and bronchospasm associated with bronchitis and emphysema. These drugs are also used to reduce uterine contractions in premature

parturition (*Partusisten*). The drugs are administered orally, parenterally or in inhalation. The duration of action of these drugs is about 6–8 hours. Side effects include nervousness, tremor, tachycardia, palpitations, headache, nausea, vomiting, and sweating. The frequency of these side effects is minimized when the drugs are given in inhalations.

Dobutamine selectively stimulates β_1-adrenergic receptors. The drug increases cardiac output owing to positive inotropic action. The drug has low influence upon the heart rate and, therefore, does not significantly increase myocardium oxygen demand. The drug is used in the treatment for acute heart failure. It should be noticed that dobutamine is used with caution in atrial fibrillation because it improves atrioventricular conduction.

Table 11 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
1	2	3
Adrenalini hydrochloridum	Subcutaneously or intramuscularly 0.0003–0.00075 g; in the eye: 1–2 drops of 1–2 % solution	Ampoules 1 ml of 0.1 % solution; 1 % or 2 % ophthalmic solution
Noradrenalini hydrotartras	Intravenously drop-by-drop 0.004–0.008 g in 1 litre of 5 % glucose solution	Ampoules 1 ml of 0.2 % solution
Mesatonum	Orally 0.01–0.025 g 2–3 times a day; subcutaneously or intramuscularly 0.003–0.005 g 1–2 times daily; intravenously 0.001–0.003 g with 40 ml of sterile isotonic NaCl solution; in the eye: 1–2 drops of 1–2 % solution	Powders for internal use; ampoules 1 ml of 1 % solution; vials 5 ml of 2.5 % ophthalmic solution
Naphthyzinum	Into the nose 1–2 drops of 0.05–0.1 % solution 3 times a day	Vials 10 ml of 0.05 or 0.1 % solution

Continuation of the table 11

1	2	3
Isadrinum	Sublingually 0.005 g; for inhalation: 1–2 inhalations of 0.5–1 % solution	Tablets 0.005 g; vials 25 ml or 100 ml of 0.5 % or 1 % solution
Salbutamol	Orally 0.002 g 3 times a day; for inhalation: 1–2 inhalations 3 times daily	Tablets 0.002 g; aerosol 10 ml
Ephedrini hydrochloridum	Orally, subcutaneously, intramuscularly, and intravenously 0.025 g 2–3 times a day	Tablets 0.025 g; ampoules 1 ml of 5 % solution

Step 1. Tasks for Self-Control
Adrenomimetic Drugs and Sympathomimetics

1. The acute attack of bronchial asthma had developed in a patient who also suffered from angina pectoris. What broncholytic should be used in this case?

A. Salbutamol.
B. Atropine sulfate.
C. Adrenaline hydrochloride.
D. Isoprenaline (isadrinum).
E. Aminophylline (euphyllinum).

2. The blood pressure had dropped in a patient receiving the halothane (phthorotanum) narcosis. What drug can be used for correction of hypotension?

A. Adrenaline.
B. Noradrenaline.
C. Mesatonum (phenylephrine).
D. Ephedrine.
E. Dopamine.

3. A drug stimulates adrenoreceptors. It is used at collapse, shock (except cardiogenic and haemorrhagic), heart arrest, hypoglycemic

coma. It is a drug of choice at anaphylactic shock. What is this drug called?

A. Noradrenaline (norepinephrine).

B. Ephedrine.

C. Isadrinum (isoprenaline).

D. Adrenaline (epinephrine).

E. Naphthyzinum (naphazoline).

4. The frequent instillation of indirect adrenomimetic into the nose at rhinitis leads to a gradual decrease of vasoconstriction. What is the name of this phenomenon?

A. Idiosyncrasy.

B. Allergy.

C. Cumulation.

D. Teratogenic action.

E. Tachyphylaxis.

5. Indicate the drug which was introduced to a patient for interruption of bronchospasm having caused tachycardia and increase of blood pressure.

A. Platyphyllin.

B. Isadrinum (isoprenaline).

C. Proserinum.

D. Salbutamol.

E. Ventolin.

6. Acute bronchospasm developed in a woman who also suffered from hypertonic disease. Prescribe the drug for interruption of acute attack of asthma for this woman.

A. Ephedrine.

B. Adrenaline.

C. Euphyllinum.

D. Salbutamol.

E. Isadrinum.

7. A patient with acute rhinitis injects drops of naphthyzinum (naphazoline) solution into the nose. Having felt improvment of condition, the patient sped up the injecting every 15–20 minutes. But

the improvment does not develop. What is the cause of this phenomenon?

A. Tachyphylaxis.

B. Cumulation.

C. Drug dependence.

D. Potentiation.

E. Sensitization.

8. A patient has acute attack of bronchial asthma. The use of which drug is the physiologically substantiated for elimination of bronchospasm?

A. Obsidan.

B. Inderal.

C. Adrenaline.

D. Phentolamine.

E. All answers are not correct.

9. What group has the mechanism of action, which is connected with accumulation of cAMP in the cells?

A. Antineoplastic antibiotics.

B. Analgesics.

C. Organic nitrates.

D. Sulfonamides.

E. β-Adrenomimetics.

10. This drug is a selective agonist of β-adrenoceptors, introduced orally and in inhalation, does not influence the heart activity. It is used for interruption and prevention of bronchospasms. Call this drug.

A. Adrenaline hydrochloride.

B. Orciprenaline (Asthmopent®).

C. Salbutamol.

D. Ephedrine hydrochloride.

E. Isadrinum (isoprenaline).

11. A patient with rhinitis injected drops of ephedrine solution into the nose. The oedema of mucous membranes has decreased. But in the result of frequent repeated introduction of solution the effect of the drug has decreased up to the complete disappearance. What is the cause of this phenomenon?

A. Introduction of a drug by wrong route.

B. Tachyphylaxis.

C. Individual tolerance to a drug.

D. Adverse effect of a drug.

E. Sensitization to a drug.

12. A doctor has introduced to a patient the drug *X* for interruption of an acute asthma attack. In the result of this introduction tachycardia and increasing of blood pressure have developed. Call the drug *X*.

A. Ventolin.

B. Euphyllinum.

C. Isadrinum (isoprenaline).

D. Platyphyllin.

E. Proserinum.

13. Prescribe to a patient with hypertensive disease the drug for prevention of acute attack of bronchial asthma.

A. Proserinum.

B. Salbutamol.

C. Adrenaline.

D. Mesatonum (phenylephrine).

E. Ephedrine.

14. Point out the adrenomimetic which in therapeutic doses causes the increase of systemic blood pressure, mydriasis, and tachycardia.

A. Salbutamol.

B. Noradrenaline (norepinephrine).

C. Mesatonum (phenylephrine).

D. Isadrinum (isoprenaline).

E. Adrenaline (epinephrine).

15. In the result of long-term using of fenoterol as broncholytic, its therapeutic activity has gradually decreased. What is the cause of tolerance developing?

A. The increase of drug elimination.

B. The increase of drug interaction with plasma albumins.

C. The decrease of β-adrenoceptors sensitivity.

D. The decrease of G_s-proteins amount.

E. The worsening of drug absorption.

16. A patient with bronchial asthma after introduction of tablet of some drug under the tongue has felt the accelerated heart rate. Point out the drug the patient has accepted.

A. Drotaverine (No-spa).

B. Isadrinum.

C. Salbutamol.

D. Papaverine.

E. Benzohexonium (hexamethonium).

17. A patient made the inhalation of some drug for interruption of acute attack of bronchospasm. The injection of this drug is also used in obstetrics for prevention of premature labour. Call this drug.

A. Euphyllinum.

B. Isadrinum.

C. Adrenaline.

D. Ephedrine.

E. Fenoterol.

18. A 45-year-old male suffers from bronchial asthma. The doctor has prescribed to him the drug in tablets, which improved the condition of the patient. But in some days the man began to complain of insomnia and increased blood pressure. What drug was prescribed to the patient?

A. Papaverine.

B. Metacinum.

C. Salbutamol.

D. Ephedrine.

E. Isadrinum.

19. Indicate the drug which is selective adrenomimetic and is used for short-term treatment of heart failure.

A. Adrenaline.

B. Dobutamine.

C. Proserinum.

D. Anaprilinum (propranolol).

E. Mesatonum.

20. A patient with hypotension had felt the worsening of condition (dizziness, weakness, and shaky gait) and accepted several tablets of

ephedrine in the short intervals of time. But some improvement the patient felt only after the first tablet. What is the cause of this phenomenon?

A. Cumulation.

B. Idiosyncrasy.

C. Tolerance.

D. Sensitization.

E. Tachyphylaxis.

21. The asthmatic status has developed in a patient. The doctor has prescribed intravenous introduction of adrenaline hydrochloride for elimination of bronchoconstriction. But its introduction has caused the worsening of condition (the increase of cyanosis, and hypoxia). What pathological mechanism is the cause of this phenomenon?

A. The increase of leukotrienes synthesis.

B. The increase of histamine releasing.

C. The decrease of α-adrenoceptor sensitivity to adrenaline.

D. The increase of β_2-adrenoceptor sensitivity to adrenaline.

E. The decrease of sensitivity of β_2-adrenoceptors to adrenaline in hypoxia condition.

22. A patient with acute rhinitis frequently injected 5 % ephedrine solution into nose. The efficacy of the drug sharply decreased and on the 3rd day completely disappeared. What is the cause of this phenomenon (tachyphylaxis)?

A. The infringement of mediator releasing from depot.

B. The progressive decrease of noradrenaline storage in sympathetic nerves.

C. The increase of reuptake of mediator.

D. The infringement of mediator synthesis in sympathetic fibers.

E. The blockade of adrenoceptors.

23. The adrenaline action is directed to the activation of enzymes group with the purpose of receiving energy. The main enzyme of this group is:

A. Phosphorylase.

B. Phosphatase.

C. Phosphofructokinase.

D. Phosphokinase.

E. Phosphomutase.

24. The inhalation drug was prescribed to a patient with bronchial asthma, which also suffered from angina pectoris. During the following inhalation the patient felt worsening of condition (tachycardia, pain in the heart area with irradiation in the left shoulder). Choose the drug which can cause such adverse effects.

A. Naphthyzinum.

B. Cromolyn sodium.

C. Fenoterol.

D. Isadrinum.

E. Euphyllinum.

25. A 13-year-old girl with the history of asthma complained of cough, dyspnea, and wheezing. Her symptoms became so severe that her parents brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnoea. Her respiratory rate was 42/min, pulse rate was 110 beats per minute, and blood pressure was 130/70 mm Hg. Choose from the following list the most appropriate drug to reverse the bronchoconstriction rapidly:

A. Cromolyn sodium.

B. Salbutamol.

C. Ipratropium.

D. Methylprednisolone.

E. Beclomethasone.

26. Spasm of smooth muscle of bronchi developed in a patient. The use of activators of what membrane cytoreceptors is physiologically valid to decrease the attack?

A. β-Adrenoreceptors.

B. α-Adrenoreceptors.

C. α- and β-adrenoreceptors.

D. M-cholinoreceptors.

E. H-cholinorceptors.

27. A patient with bronchial asthma had been taking tablets which caused insomnia, headache, and increased blood pressure. What drug can cause such complication?

A. Chromolyn sodium.

B. Isadrinum.

C. Euphyllinum.

D. Adrenaline.

E. Ephedrine.

28. An emergency doctor was called to a 40-year-old patient with bronchial asthma, who had an attack of bronchospasm with manifestations of angina pectoris. What drug is the most effective for the acute care?

A. Platyphyllin hydrotartrate.

B. Salbutamol.

C. Ephedrine hydrochloride.

D. Adrenaline hydrochloride.

E. Atropine sulfate.

29. A patient came to a doctor complaining of health state deterioration. While waiting he had an attack of bronchial asthma. Drugs of what group are expedient for the first aid?

A. β-Adrenoreceptor agonists.

B. β-Adrenergic blockers.

C. N-cholinominetics.

D. M-cholinominetics.

E. Sympatholytics.

30. During an operative intervention with additional use of hygronium the patient's arterial pressure has sharply decreased. What groups of drugs can normalize the arterial pressure in the given situation?

A. N-cholinomimetics.

B. β-Adrenergic blockers.

C. Ganglionic blockers.

D. α-Adrenomimetics.

E. M-cholinoblockers.

31. A 63-year-old man was admitted to an emergency hospital in a collaptoid state. In order to cure hypotension, the doctor chose noradrenaline hydrotartrate. What is the mechanism of the hypertensive action of this drug?

A. Inhibition of M-cholinoreceptors.

B. Activation of α_1-adrenoceptors.

C. Activation of serotoninergic receptors.

D. Activation of β-adrenoceptors.

E. Activation of dopamine receptors.

32. Some therapeutic agent has the following characteristics: synthetic catecholamine, stimulates β_1- and β_2-adrenoceptors, activates the work of the heart, determines the increase of heart rate. But it can lead to the suppression of birth activity and to the decrease of arterial pressure. It is a pharmacological antagonist of propranolol. What is this drug?

A. Cytitonum.

B. Carbacholine.

C. Aceclidine.

D. Pilocarpine hydrochloride.

E. Isadrinum.

33. With a diagnostic purpose (pupil dilation for the inspection of the eye ground) an ophthalmologist used 1 % solution of mesatonum. Mydriasis, brought on by the drug, is the result of:

A. Activation of M-cholinoreceptors.

B. Activation of β_2-adrenoreceptors.

C. Activation of α_1-adrenoreceptors.

D. Blockade of α_1-adrenoreceptors.

E. Activation of β_1-adrenoreceptors.

34. A patient in the condition of acute circulatory collapse resulting from severe poisoning with unknown substance has been admitted to the hospital. What drug should be used for the acute care?

A. Propranolol.

B. Mesatonum.

C. Naphthyzinum.

D. Isadrinum.

E. Salbutamol.

35. A 42-year-old patient has bronchial asthma. To relieve the attacks of bronchospasm a doctor has prescribed salbutamol. What is its medicinal effect?

A. Stimulation of α_1-adrenoreceptors.

B. Stimulation of β_2-adrenoreceptors.

C. Blockade of β_2-adrenoreceptors.

D. Stimulation of α_2-adrenoreceptors.

E. Stimulation of β_1-adrenoreceptors.

36. A patient has anaphylactic shock. From which of adrenoreceptor agonists is it possible to accept the maximal therapeutic effect?

A. Alupent.

B. Mesatonum.

C. Ephedrine hydrochloride.

D. Noradrenaline hydrotartrate.

E. Adrenaline hydrochloride.

37. A patient has a collaptoid state because of the peripheral vessels tone decrease. What drug is the most effective in this situation?

A. Prazosin.

B. Proserinum.

C. Mesatonum.

D. Isadrinum.

E. Clophelinum.

38. A patient visiting a traumatologist had acute arterial hypotension. Which of the drugs stimulating adrenergic innervation would you suggest for normalization of arterial pressure?

A. Xylometazoline.

B. Prazosin.

C. Naphthyzinum.

D. Doxazosin.

E. Mesatonum.

39. During the tooth extraction a patient had bleeding. The dentist imposed a tampon with a medicine, and the bleeding decreased. What drug was used by the doctor?

A. Cromolyn sodium.

B. Isadrinum.

C. Adrenaline hydrochloride.

D. Naphthyzinum.

E. Octadinum.

40. A broncholytic drug that stimulates β_2-adrenergic receptors is prescribed to a patient with obstructive bronchitis. Specify this medication.

A. Prednisolone.

B. Salbutamol.

C. Cromolyn sodium.

D. Euphyllinum.

E. Metacinum.

41. The anaphylactic shock has developed in a patient during local anaesthesia concerning tooth extraction. Choose the drug for interruption of this condition.

A. Atropine sulfate.

B. Euphyllinum.

C. Cordiaminum.

D. Dimedrol.

E. Adrenaline hydrochloride.

42. The acute vessels insufficiency has developed in a 58-year-old patient in the result of overdosing of vessels-widening drug. What drug should be used for elimination of this condition?

A. Noradrenaline.

B. Caffeine.

C. Euphyllinum.

D. Dopamine.

E. Cordiaminum.

43. In experiments on live sections of a liver, the substance addition to medium solution has caused increasing of secretion of glucose. This substance effect is reduced by anaprilinum. What substance is it?

A. Adrenaline.

B. Dobutamine.

C. Isadrinum.

D. Fenoterol.

E. Mesatonum.

44. A female with hypoglycaemic coma is delivered to an urgent department. What drug should be prescribed to this patient?

A. Clophelinum.

B. Pilocarpine hydrochloride.

C. Aminazine.

D. Adrenaline hydrochloride.

E. Biseptol.

45. The broncholytic drug is prescribed to a patient for prevention of bronchial asthma attacks. What drug is prescribed?

A. Anaprilinum.

B. Noradrenaline.

C. Metronidazole.

D. Salbutamol.

E. Proserinum.

46. The bitten by a bee patient with the signs of anaphylactic shock is delivered to an emergency room. What drug should be introduced to the patient?

A. Ranitidine.

B. Isoniazid.

C. Adrenaline hydrochloride.

D. Clotrimazole.

E. Sulfadimethoxine.

Antiadrenergic Agents

Drugs which block adrenergic receptors are called adrenoblockers or adrenergic antagonists. These agents prevent or eliminate the corresponding effects of adrenomimetics owing to the blockade of certain types of adrenergic receptors.

According to two families of adrenergic receptors, adrenergic antagonists are classified into α-adrenergic antagonists (α-adrenoblocking drugs), β-adrenergic antagonists (β-adrenoblocking drugs), and α, β-adrenergic antagonists (α,β-adrenoblocking drugs). Also, there is a group of sympatholytics.

Classification of adrenergic antagonists

1. α-Adrenoblocking drugs:

a) $\alpha_{1,2}$-adrenoblocking drugs: *phentolamine (regitine), tropaphenum,* and *pirroxane*;

b) α_1-adrenoblocking drugs: *prazosin (minipress), terazosin,* and *doxazosin (cardura)*;

c) α_2-adrenoblocking drugs: *yohimbine.*

2. β-Adrenoblocking drugs:

a) $\beta_{1,2}$-adrenoblocking drugs: *anaprilinum (propranolol), nadolol, sotalol, oxprenolol,* and *pindolol*;

b) β_1-adrenoblocking drugs: *metoprolol, talinolol, atenolol, nebivolol,* and *acebutalol.*

3. α, β-Adrenoblocking drugs: *labetalol, proxodolol,* and *carvedilol.*

4. Sympatholytics: *reserpine, octadinum (guanethidine),* and *ornidum (bretylium tosilate).*

α-Adrenoblocking Drugs

The drugs of this group compete with catecholamines for binding with α-adrenergic receptors in tissues. These agents more readily prevent or eliminate the α-adrenergic effects of adrenaline than those of noradrenaline. The α-adrenergic antagonists reverse the effects of adrenaline mediated by excitation of α-adrenergic receptors. Thus, the vasoconstrictive action of adrenaline is interrupted, but vasodilation

caused by stimulation of β-receptors is not blocked. Therefore, the systemic blood pressure decreases due to the epinephrine administration on the background of preliminary administration of α-adrenoblocking agent. This phenomenon is called "epinephrine reversal".

Phentolamine (regitine) competitively blocks both α_1- and α_2-adrenergic receptors. Intravenously administered phentolamine causes short-time hypotension (10–15 minutes). The blood flow in vessels of skin, mucosa, and partly in vessels of skeletal muscles is increased. The vascular effects of phentolamine are used in the treatment for obliterating endarteritis and Raynaud's disease and disorders associated with them (shin ulcers, atrophic rhinitis, and degenerative retinal changes). Also, phentolamine is used to treat acute heart failure, hypertensive crisis, and pheochromocytoma. Pheochromocytoma is a hormonal active tumor of adrenal medulla which produces and releases adrenaline into the blood, and less – noradrenaline. This disease is characterized by periodical attacks of tachycardia and hypertensive crisis. α-Adrenoblockers are the active drugs for treatment and diagnostics of pheochromocytoma because adrenaline (but not noradrenaline) plays the leading role in genesis of this disease. α-Adrenoblockers are also used to reduce vascular spasm at traumatic shock. This pathology is accompanied by the stable activation of sympathetic nervous system that leads to the marked vasoconstriction. In this situation, α-adrenoblocker administration prevents ischemia of tissues, acidosis, and focal necrosis.

The indications for therapeutic use of *tropaphenum* and *pirroxane* are identical with those of phentolamine. There are evidences that tropaphenum decreases platelet aggregation and viscosity of arterial and venous blood.

Except peripheral adrenergic receptors, *pirroxane* also blocks the central ones. Therefore, it is also used in treatment for hypertension with diencephalic pathology. Pirroxane diminishes psychical tension and anxiety and prevents the vomiting of vestibular origin (at motion sickness and Meniere's syndrome). Also, pirroxane is used to reduce

manifestations of withdrawal syndrome that developed in addicts owing to the termination of administration of morphine and ethyl alcohol.

After parenteral administration of α-adrenoblockers, a patient should lie for 2–3 hours to prevent postural hypotension.

The overdose of α-adrenoblockers leads to orthostatic collapse, tachycardia, disorders of the heart rhythm, increased myocardial oxygen demand, nausea, increased secretion of exocrine glands, and diarrhea.

Interest to α-adrenoblockers has grown in relation to synthesis of drugs that selectively act upon α_1-adrenergic receptors (*prazosin, terazosin, tamsulosin, doxazosin, alfuzosin, nicergoline*). These drugs don't cause marked tachicardia and increase of myocardium oxygen consumption because agents don't affect the negative feedback associated with the blockage of presynaptic α_2-adrenoceptors. Therefore, the vasodilator effect of α_1-adrenergic antagonists is stable in a long-term use.

α_1-Adrenoblockers exhibit mainly indirect action upon the heart. These drugs decrease the afterload upon the left ventricle due to the dilation of peripheral vessels and reduction of peripheral resistance. The blood pressure in pulmonary circulation is reduced. The preload (venous blood return) is also slightly decreased. These changes provide the decrease of the heart work and oxygen consumption of myocardium. Thus, α_1-adrenergic antagonists facilitate the heart work and are used in the treatment for chronic heart failure. Many therapists consider α_1-adrenoblockers as alternative to cardiac glycosides because they are safer.

Duration of action of *Prazosin* is 6–8 hours in case of oral intake. Also, the drug exhibits antiatherosclerotic action. Prazosin is used to interrupt hypertensive crisis, to treat pulmonary hypertension, hypertensive disease, and disorders of peripheral blood circulation.

Nicergoline is used in the treatment for cerebrovascular insufficiency.

Terazosin and *doxazosin* selectively block α_{1A}-adrenergic receptors. These drugs are used to treat arterial hypertension and prostate adenoma. The blockage of α_{1A}-adrenoceptors relaxes the smooth muscles of prostate, bladder neck, and prostatic part of the urinary tract that improves the urination.

Tamsulosin exerts significantly higher affinity to α_{1A}-adrenergic receptors than to α_{1B}-adrenoceptors. The drug is used in the treatment for benign prostatic hyperplasia and chronic prostatitis.

Yohimbine selectively blocks α_2-adrenergic receptors. The drug easily penetrates the central nervous system and exhibits antidepressive and psychistimulative effects. Yohimbine stimulates the sexual potency in men. The drug is manufactured in tablets and is used to treat the erectile dysfunction.

β-Adrenergic Antagonists

β-Adrenergic antagonists (β-adrenoblockers) are drugs which selectively bind with β-adrenergic receptors of the heart, vessels, bronchi, uterus, and other organs and prevent their excitation by catecholamines.

Depending on the selectivity to certain types of β-adrenergic receptors, β-adrenergic antagonists are classified as follows:

1) β_1- and β_2-adrenoblockers (non-selective β-adrenoblockers): *anaprilinum (propranolol), nadolol, sotalol, oxprenolol,* and *pindolol*;

2) β_1-adrenoblockers (cardioselective β-adrenoblocklers): *metoprolol, talinolol, atenolol, nebivolol,* and *acebutalol.*

Due to blockage of β_1-adrenergic receptors located in sinoatrial node, β-adrenergic antagonists decrease heart rate (negative chronotropic action). Blockage of β_1-adrenergic receptors of atrioventricular node leads to slowdown of impulse conduction

(negative dromotropic action). Also, β-adrenergic antagonists are negative inotropic agents (decrease the force of heart contraction).

The action of β-adrenoblockers upon the blood pressure is complex. β-Adrenoblockers decrease the renin secretion owing to blockage of β_1-adrenergic receptors which are located in the cell membranes of juxtaglomerular apparatus. It leads to the reduction of production of angiotensin II and aldosterone with the following lowering blood pressure. The decrease of cardiac output also provides the hypotensive effect. Non-selective β-adrenergic antagonists block presynaptic β_2-adrenoceptors that leads to the decrease of noradrenaline release that also promotes the lowering of blood pressure. Lipophilic β-adrenergic antagonists exhibit the additional mechanism of antihypertensive action that is associated with the blockage of β-adrenoceptors in the central nervous system.

β-Adrenoblockers decrease intraoccular pressure because blockage of β_1-adrenergic receptors suppress the production of aqueous humour by the ciliary body.

The blockage of β_2-adrenergic receptors of smooth muscles is manifested by the increase of bronchial, uterine, and vascular tone.

β-Adrenergic antagonists antagonize metabolic effects of catecholamines. Under their influence, the catabolism of lipids and glycogen is suppressed, the body temperature is lowered, the level of Ca^{2+} ions in cardiomyocytes and in skeletal muscles is decreased, but the intracellular calcium concentration in smooth muscles is increased.

Nowadays, β-adrenergic antagonists play the significant role in the treatment of ischemic heart disease, myocardial infarction, tachyarrhythmias, and hypertensive disease.

The β-adrenoblockers are characterized by some specific properties, which influence the peculiarities of their clinical use.

1. Selective or non-selective β-adrenoblockering activity. The agents with selective action upon β_1-adrenergic receptors (such as metoprolol, talinolol, atenolol, etc.) are most valuable for cardiology. The parallel blockage of β_2-adrenoceptors as a rule is undesirable and can cause such complications as reduction of coronary blood flow, impairment of blood flow in extremities, and spasm of bronchi.

2. Intrinsic sympathomimetic activity. It is the ability of drugs to show the moderate and stable β-adrenomimetic activity along with the ability to block the excessive influence of catecholamines upon the heart. Such drugs (pindolol, acebutalol, etc.) have less apparent ability to provoke the left ventricular insufficiency due to the loss of adaptive tonic function of sympathetic nervous system.

3. Membrano-stabilizing activity (propranolol, pindolol, metoprolol, etc.). This effect is a result of the blockade of sodium channels. It is like the action of local anesthetics. Membrano-stabilizing action of β-adrenoblockers is manifested in the conductive system of the heart and neurons.

Thus, the ability to block β_1-adrenergic receptors is the main property of β-adrenergic antagonists. It leads to reduction of sympathoadrenal control of the heart functions manifested by prevention or elimination of tachycardia, lowering of elevated oxygen demand of the heart, and reduction of neurogenic disorders of the heart rate. The heart contractility also decreases but in less degree. In patients with masked insufficiency of left ventricle, it can provoke a heart failure due to physical activity.

β-Adrenoblockers protect the heart from the influence of stress and negative emotions. These drugs also eliminate the active influence of sympathetic innervation upon the speed of impulse conduction in the conductive system, especially through the atrioventricular node. β-Adrenoblockers increase the possibility of conduction blockages. Drugs with intrinsic sympathomimetic activity are less dangerous in this respect.

There are the following indications for clinical use of β-adrenoblockers:

1. Cardiac tachyarrhythmias including those requiring urgent care.

2. Angina pectoris. Selective β_1-adrenergic antagonists are more valuable in the treatment for ischemic heart disease, especially in patients who have bronchial asthma or spasm of peripheral vessels in anamnesis.

3. Group of β-adrenergic antagonists is one of the basic groups for treatment of hypertensive disease.

4. Treatment of hyperthyroidism. β-Adrenoblockers eliminate the peripheral manifestations of hyperthyroidism, such as tachycardia, increased cardiac output, and muscle tremors.

5. β-Adrenergic antagonists (timolol, betaxolol, etc.) are used topically to reduce intraocular pressure in patients with glaucoma.

6. Lipophilic β-blockers are used to treat neurosis and migraine. At migraine, the blockade of cerebrovascular β-receptors reduces the vasodilation and pain.

7. Propranolol is used to reduce uterine bleeding at parturition and in postoperative period.

Side effects of β-adrenoceptor antagonists are bradycardia, conduction disturbances, arterial hypotension, heart failure, bronchoconstriction, worsening of lipid spectrum (drugs increase the level of atherogenic lipoproteins), central nervous system suppression, hypoglycemia, vasospasm of limbs, and dyspeptic disorders.

Sudden interruption of β-adrenoceptor antagonist intake after a long-time therapy can result in return syndrome that manifests by hypertensive crisis, angina attacks, and tachyarrhythmias. Phasing out the drug with a different treatment regimen is the easiest and safest way to prevent relapse syndrome.

α- and β-Adrenoblockers

Labetalol (*Trandate*) is α_1-, β_1-, and β_2-adrenergic receptor antagonist. The ratio of β- to α-receptor blocking activity is about 3:1 when labetalol is administered orally and about 7:1 if the drug is administered intravenously. The blocking ability of labetalol is significantly less than those of phentolamine and propranolol (2–7 times, but according to some data – 5–18 times). Due to the blockage of vascular α_1-adrenoceptors, labetalol reduces the blood pressure and after-load upon the heart, that accompanied by insignificant changes of the heart rate and cardiac output because the drug also blocks β_1-adrenoceptors of the heart.

Antihypertensive effect of labetalol is mainly determinated by its influence upon the vessels and is gradually developed. Labetalol is used both to treat hypertensive disease and to interrupt hypertensive crisis. Also, labetalol is used in the treatment for pheochromocytoma and moderately severe heart failure. The drug can provoke postural hypotension.

Sympatholytics

Sympatholytics are drugs with presynaptic action which affect the synthesis, release, and deposition of noradrenaline. These drugs eliminate the effects of excitation of sympathetic nerves, but do not prevent the effects of exogenous adrenaline and noradrenaline. It should be noticed that these drugs cause sympathetic blockage at the presynaptic level. The most important part of their pharmacodynamics is their influence upon the cardiovascular system. Sympatholytics exhibit antihypertensive effect that is the base for their clinical use in the treatment for hypertensive disease. This group includes *reserpine, octadinum* (*guanethidine*), and *ornidum* (*bretylium*).

Reserpine is a plant alkaloid derived from rauwolfia. This drug blocks the deposition of noradrenaline into the vesicles of adrenergic nerve endings that leads to mediator inactivation by MAO. On the other hand, reserpine stimulates the noradrenaline release by presynaptic membrane. It can cause the initial adrenomimetic effect which is, however, weakly expressed. Besides, reserpine inhibits the synthesis of noradrenaline.

Thus, reserpine exhausts the mediator depot that leads to reduction of adrenergic influence upon inner organs. It should be noticed that adrenergic function is reduced when the depot of noradrenaline is decreased by 2/3 that needs some time. Therefore, sympatholytic action of reserpine begins to develop only in several hours. Maximal effect develops in 3–4 days after the start of drug intake. After termination of the drug intake, its effects persist for many

days, because partial recovery of mediator level occurs in about a week and full recovery of mediator depot develops in 2–3 weeks.

Reserpine easily penetrates the central nervous system and exhibits its action in adrenergic and serotoninergic synapses. The drug exhibits sedative and weak antipsychotic effects due to which it is also included to the group of neuroleptics.

Reserpine is used to treat hypertensive disease, mainly its initial form and cases of moderate severity. Also, the drug is seldom used in the treatment of tachyarrhythmias.

Side effects of reserpine are associated with predominat influence of cholinergic innervation: bradycardia, elevation of secretion and motility of gastrointestinal tract (diarrhea, gastritis), nasal congestion, drowsiness, weakness, depression, pain in the area of a parotid gland, and decreased libido in men. Reserpine increases the possibility of breast cancer in women.

Octadinum (*guanethidine*) reduces the depot of noradrenaline owing to the stimulation of mediator release by presynaptic membrane, lowering of mediator redeposition, and inhibition of noradrenaline synthesis. But the main part of octadinum action is blockage of noradrenaline reuptake by presynaptic nervous endings that leads to inactivation of mediator by COMT. The first administration of octadinum can result in short-time sympathomimetic effects (elevation of blood pressure and tachycardia) which is replaced by the following inhibition of sympathetic activity. Octadinum does not penetrate in the central nervous system and lacks the central effects.

Octadinum is used to treat hypertensive disease of moderate severity and severe its forms. Due to possibility of orthostatic collapse, octadinum is used mainly to treat inpatients. Sometimes, octadinum is used in the treatment of glaucoma. Side effects of octadinum are identical to side effects of reserpine. Besides, octadinum can cause orthostatic collapse.

Ornidum blocks the noradrenaline release without influence upon mediator depot. Its use is accompanied by different side effects,

besides its hypotensive effect is characterized by fast development of tolerance. Therefore, ornidum is not used in treatment of hypertensive disease. The drug is used as reserve agent to treat ventricular tachyarrhythmias.

Sympatholytics are contraindicated at severe organic cardiovascular diseases, marked renal failure, and ulcer disease of stomach and duodenum. Octadinum is not recommended for pheochromocytoma.

It should be noticed, that in recent years, clinical use of sympatholytics in the treatment for arterial hypertension was significantly restricted.

Table 12 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
Phentolamini hydrochloridum	Orally 0.05 g 3–5 times a day	Tablets 0.025 g
Tropaphenum	Subcutaneously or intramuscularly 0.01–0.02 g 1–3 times a day; intravenously 0.01 g	Ampoules 0.02 g of powder for injection (before administration the powder of 1 ampoule is dissolved in 1–2 ml of sterile water)
Prazosinum	Orally, 0.0005–0.002 g 3–4 times a day	Tablets 0.001; 0.002 or 0.005 g
Anaprilinum	Orally 0.01–0.04 g 3–4 times a day; intravenously slowly 0.001 g	Tablets 0.01 or 0.04 g; ampoules 1 or 5 ml of 0.1 % solution
Metoprololum	Orally 0.05–0.1 g 2–4 times a day; intravenously slowly 0.005–0.015 g	Tablets 0.05 or 0.1 g ampoules 5 ml of 1 % solution
Talinololum	Orally 0.05–0.1 g 3 times a day	Dragee 0.05 g
Octadinum	Orally 0.025–0.05 g once a day	Tablets 0.025 g
Reserpinum	Orally 0.00005–0.0001 g 1–3 times a day	Tablets 0.0001 or 0.00025 g

Step 1. Tasks for Self-Control
Antiadrenergic Drugs

1. A doctor prescribed the antihypertensive drug to a patient, who suffers from hypertensive disease and obstructive bronchitis. After some time, asthma attacks have arisen in the patient and expressed bradycardia has developed. In ECG the signs of AV blockade were observed. Choose the drug for which these adverse effects are most common.

A. Reserpine.

B. Clophelinum (clonidine).

C. Talinolol (Cordanum).

D. Verapamil.

E. Anaprilinum (propranolol).

2. A doctor prescribed the antihypertensive drug to a patient, who suffers from hypertensive disease and obstructive bronchitis. After some time, asthma attacks have arisen in the patient. What is the cause of this adverse effect?

A. Stimulation of bronchial α_1-adrenoceptors.

B. Blockade of bronchial β_1-adrenoceptors.

C. Blockade of bronchial β_2-adrenoceptors.

D. Stimulation of bronchial β_2-adrenoceptors.

E. Blockade of bronchial α_2-adrenoceptors.

3. A patient suffering from bronchial asthma is staying in the hospital. Hypertonic disease is diagnosed as accompanying disease. Indicate the drug, which is contraindicated to this patient.

A. Ephedrine hydrochloride.

B. Anaprilinum (propranolol).

C. Papaverine hydrochloride.

D. Atropine sulfate.

E. Salbutamol.

4. A patient with pheochromocytoma suffers from increased blood pressure which develops at hypertensive crisis. What drug group is useful in this case?

A. α-Adrenoblockers.

B. Blockers of Ca^{2+} channels.

C. β-Adrenoblockers.

D. Ganglion blockers.

E. Sympatholytics.

5. Rapid and significant decrease of blood pressure is the main way of interruption of hypertensive crisis. The injection of which group of antiadrenergic drugs is used for this purpose?

A. α-Adrenoblockers.

B. Non-selective β-adrenoblockers.

C. Cardioselective β-adrenoblockers.

D. Sympatholytics.

E. All answers are incorrect.

6. Bronchospasm has developed in a patient with angina pectoris after taking antihypertensive drug. What drug was taken by the patient?

A. Dipyridamole.

B. Nitroglycerin.

C. Sustac forte.

D. Nifedipine.

E. Propranolol (anaprilinum).

7. A doctor has prescribed propranolol to a 36-year-old female with ischaemic heart disease. But having found out the presence of accompanying disease, the doctor replaced propranolol by atenolol. What disease is the cause of this replacement?

A. Cholecystitis.

B. Arterial hypertension.

C. Bronchial asthma.

D. Ulcer disease of duodenum.

E. Myasthenia.

8. A 60-year-old female suffers from toxic goiter and complains of a tachycardia. What drug should be prescribed for normalization of cardiac rhythm?

A. Pentamine.

B. Isadrinum (isoproterenol).

C. Salbutamol.

D. Anaprilinum (propranolol).

E. Adrenaline (epinephrine).

9. A patient with diabetes mellitus has taken the dose of long-acting insulin in the morning but did not take food. After some time, the patient has got the following signs: weakness, headache, dizziness, trembling, and convulsions. What drug should be introduced for interruption of hypoglycemia?

A. Hydrocortisone.

B. Triamcinolone.

C. Adrenaline.

D. Noradrenaline.

E. Prednisolone.

10. A patient with ischemic heart disease did not inform the doctor, that he had attacks of bronchospasm. The doctor prescribed the drug *A* to him. After that the attacks of angina pectoris became rare, but attacks of bronchospasm became more often. Point out the drug, which was prescribed to the patient.

A. Nitrosorbide.

B. Atenolol.

C. Anaprilinum (propranolol).

D. Verapamil.

E. Diltiazem.

11. Broncho-obstructive syndrome (deterioration of breathing, cough) has developed in a patient during the treatment of ciliary arrhythmia. Indicate the antiarrhythmic drug which can cause such complication.

A. Novocainamidum (procainamide).

B. Ajmalin.

C. Nifedipine.

D. Verapamil.

E. Anaprilinum (propranolol).

12. A doctor has prescribed anaprilinum to a patient who suffers from hypertensive disease. In two weeks from the start of treatment the patient began to complain of asthma feeling and deterioration of breathing. Explain the possible cause of this complication and doctor's tactics in this case.

A. Allergic reaction. To cancel anaprilinum and prescribe H_1-histaminoblockers.

B. Blockade of β_1-adrenoceptors. To prescribe selective β_2-adrenoblocker.

C. Myotropic bronchospastic action. To prescribe euphyllinum (aminophylline).

D. Excitation of M-cholinoceptors. To prescribe atropine.

E. Blockade of β_2-adrenoceptors. To prescribe selective β_1-adrenoblocker.

13. A 50-year-old female suffers from hypertensive disease and ulcer disease of stomach with increased production of hydrochloric acid. Indicate the drug which is contraindicated to this patient for treatment of hypertensive disease.

A. Nifedipine (phenygidine).

B. Dibazol.

C. Spironolactone.

D. Reserpine.

E. Furosemide.

14. A 50-year-old patient suffers from ischemic heart disease, ciliary arrhythmia, and cardiosclerosis. Choose the drug which is necessary to prescribe to this patient.

A. Potassium chloride.

B. Metoprolol.

C. Acetylsalicylic acid.

D. Digoxin.

E. Strophanthin.

15. A patient who suffers from hypertensive disease of the I stage, took the drug *A* in tablets. In several weeks he began feeling pain in stomach, nausea, apathy, sleepiness. What drug is the cause of these adverse effects?

A. Reserpine.

B. Captopril.

C. Chlorothiazide (dichlothiazidum).

D. Octadinum.

E. Phenygidine.

16. It is necessary to prescribe antiarrhythmic drug to a patient who suffers from ciliary arrhythmia and bronchial asthma. Indicate antiarrhythmic drug which is contraindicated to this patient.

A. Novocainamidum (procainamide).

B. Ajmalin.

C. Verapamil.

D. Nifedipine.

E. Anaprilinum (propranolol).

17. Anaprilinum therapy caused a positive effect in the dynamic of the disease of a 44-year-old woman suffering from stenocardia. What is the main mechanism of the effect of this drug?

A. Decrease of oxidative exchange in myocardium due to enzyme blockade of Krebs cycle.

B. Increased oxygen supply to the myocardium.

C. Decreased power inputs of myocardium due to reduced loading.

D. Decreased need in increasing of oxygen supply to the myocardium.

E. Blockade of β-adrenoceptors and decrease of myocardial requirements to the oxygen.

18. Propranolol has been prescribed to a 36-year-old female patient suffering from ischemic heart disease. But the doctor decided to replace this drug by atenolol due to concomitant disease. What disease was found by the doctor?

A. Cholecystitis.

B. Bronchial asthma.

C. Arterial hypertension.

D. Duodenal ulcer.

E. Myasthenia.

19. A 60-year-old woman, suffering from toxic goiter, complains of constant palpitation. What drug should be prescribed for normalization of heart rate?

A. Pentamine.

B. Isadrinum.

C. Propranolol.

D. Salbutamol.

E. Adrenaline hydrochloride.

20. For the treatment of angina a selective β_1-adrenergic blocker, which has no internal sympathomimetic activity, was prescribed. It is known that the drug is lipophilic, has average duration of action and is produced in tablets and ampoules. What is this drug?

A. Metoprolol.

B. Propranolol.

C. Talinolol.

D. Benzohexonium.

E. Drotaverine.

21. Therapy with propranolol has positively affected the course of the disease of a 44-year-old woman with angina pectoris. What is the mechanism of antianginal action of this drug?

A. Decrease of the need for oxygen and increase of the coming of oxygen into the myocardium.

B. Decrease of the oxidative exchange in the myocardium due to the inhibition of the enzymes of Krebs cycle.

C. Decrease of myocardium energy consumption due to the decrease of load.

D. Increase of oxygen coming into the myocardium.

E. Inhibition of β_1-adrenoceptors and decrease of the need of the myocardium for oxygen.

22. A patient suffering from ischemic heart disease did not inform the doctor about the attacks of bronchospasm he sometimes had, the doctor prescribed a drug, the intake of which made the attacks of angina pectoris less frequent, but the attacks of bronchospasm became more frequent. What drug has been prescribed?

A. Propranolol.

B. Diltiazem.

C. Verapamil.

D. Nitrosorbide.

E. Nitroglycerin.

23. For the treatment of ischemic heart disease a patient has been given β-adrenoreceptor antagonist. After a while he had a cough and bronchospasm. Which of the drugs has such evident side action?

A. Metoprolol.

B. Talinolol.

C. Atenolol.

D. Propranolol.

E. Nifedipine.

24. Bronchoconstriction has developed in a hypertensive patient after an intake of a drug. What drug causes bronchoconstriction?

A. Isosorbide mononitrate.

B. Nitroglycerin.

C. Corglycon.

D. Propranolol.

E. Amiodarone.

25. Antihypertensive agent has decreased the blood pressure during first several days of treatment owing to reducing the minute heart volume. In four weeks of using, the minute heart volume restored to an initial level but the blood pressure remained low. Indicate the drug which is used in this case.

A. Losartan.

B. Prazosin.

C. Anaprilinum.

D. Methyldopa.

E. Octadinum.

26. Drag *A* is prescribed to a patient with ischemic heart disease for prevention of angina attacks. Indicate this drug.

A. Metoprolol.

B. Furosemide.

C. Atropine sulfate.

D. Morphine.

E. Oxytocin.

27. A patient with hypertensive disease is delivered to a cardiologic department. The doctor prescribed him the hypotensive drug which blocks both β_1- and β_2-adrenoceptors. Indicate this drug.

A. Indomethacin.

B. Proserinum.
C. Celecoxib.
D. Prednisolone.
E. Anaprilinum.

28. A patient with coronary artery disease was admitted to the cardiological department. For stenocardia prevention a drug from the group of β-adrenoceptor blockers was administered. What drug is it?

A. Atropine sulfate.
B. Morphine hydrochloride.
C. Metoprolol.
D. Oxytocin.
E. Furosemide.

DRUGS INFLUENCING CENTRAL NERVOUS SYSTEM

General Anaesthetics

General anaesthetics induce reversible physiological state which is characterized by analgesia, loss of consciousness and all types of sensitivity, inhibition of reflexes, and skeletal muscle relaxation. In Greek, the word anaesthesia meens "an" – "without" and "aesthēsis" – "sensation".

General anaesthetics differ in their chemical and physical characteristics and in the usual routes of administration.

General anaesthetics are classified as follows:

1. Inhalational general anaesthetics.

1.1. Volatile liquids: *diethyl ether, halothane (fluothane), enflurane, sevoflurane,* and *isoflurane.*

1.2. Gases: *nitrous oxide (N_2O).*

2. Intravenous anaesthetics.

2.1. Drugs with short duration of action: *propanidid (sombrevin)* and *ketamine (ketalar).*

2.2. Drugs with intermediate duration of action: barbituric acid derivatives *thiopental sodium* and *hexenalum (hexobarbital)*;

2.3. Drugs with long duration of action: *sodium oxybutyrate (oxybate sodium).*

The phenomenon of general anaesthesia was discovered in 1846, when Morton showed the use of ether as a general anaesthetic. Many other general anaesthetics have been derived later and are available for use nowadays.

Mechanism of Action

All effects of general anaesthetics are associated with the inhibition of synaptic impulces transmission on the different levels of the central nervous system: cerebral cortex, diencephalon, midbrain, spinal cord, etc. There are different theories which explain the mechanisms of action of general anaesthetics: coagulative, proteinic, lipoid, absorption, thermodinamic theory, etc. But none of them can explain the mechanism of action of all general anaesthetics at the

neuronal level. It should be noticed that mechanisms of anaesthetic effect can significantly differ for different drugs due to their different chemical structure.

General anaesthetics are built in the neuronal membranes and change their structure and function of sodium and calcium channels. The following reduction of intracellular sodium results in reduction of neuronal excitability. Reduction of intracellular calcium concentration affects the release of mediators by presynaptic membranes. Due to this, the activity of adrenergic transmission in the central nervous system decreases with simultaneous activation of GABA-ergic and opioidergic activity. Besides, general anaesthetics inhibit dopaminergic, cholinergic, and serotoninergic transmission in the central nervous system.

There are general anaesthetics which exhibit anaesthetic activity due to interaction with certain receptors. Thus, derivatives of barbituric acid bind to barbiturate receptors which are the part of benzodiazepine-barbiturate-GABA receptor complex. It results in an increase of sensitivity of $GABA_A$-receptors to GABA with the following opening of chlorine channels and hyperpolarization of neuronal membrane. Ketamine is antagonist of N-methyl-D-aspartic acid (NMDA) receptors. At the same time, the action mechanism of diethyl ether, nitrous oxide, halothane and other inhalational anaesthetics is not associated with specific influence upon the certain receptors. Anaesthetic effects of these drugs result from their interaction with neuronal membranes in the central nervous system. Independently from the mechanism of action, the final result of action of all drugs is inhibition of synaptic transmission of excitement in the central nervous system.

The state of general anaesthesia is divided into the following stages:

I – Stage of analgesia.

II – Stage of excitement.

III – Stage of surgical anaesthesia which is divided into 4 levels:

– 1^{st} level – superficial anaesthesia;

– 2nd level – light anaesthesia;
– 3rd level – deep anaesthesia;
– 4th level – super-deep anaesthesia.
IV – Stage of respiratory paralysis (overdose).

It is the general scheme of anaesthesia, but it can differ for different drugs.

Inhalational Anaesthetics

The inhalational anaesthetics are divided into two groups depending on their physical properties: gases (nitrous oxide and cyclopropane) and volarile liquids (diethyl ether, halothane, etc.).

Inhalational anaesthetics require the special anaesthesia machine for their dosage. At inspiration, anaesthetics are absorbed in the blood from the lungs and distributed into the different tissues. The higher drug concentration increases in the blood and tissues, the faster general anaesthesia develops. This process depends on concentration of a drug in the inhaled air, frequency and depth of respiration, solubility of anaesthetic in the blood and other factors.

There are certain requirements to general anaesthetics:
– drugs should not irritate mucous membranes;
– anaesthesia should develop quickly and without stage of excitement;
– anaesthesia should be easily manageable;
– anaesthetic should not cause toxic and side effects;
– period of recovery should be short, without afteraction;
– anaesthetic should be fire-safe.

Diethyl ether is volatile liquid with irritative properties. High activity and relatively low toxicity of diethyl ether allow to achieve the necessary depth of anaesthesia and relaxation of skeletal muscles at sufficient oxygen concentration in inhaled air. Ether anaesthesia is easily manageable.

The ether anaesthesia is characterized by all well expressed stages of anaesthesia.

The stage of analgesia lasts for 1–3 minutes. This stage begins with the start of anaesthetic inhalation and lasts to the loss of

consciousness. It is manifested by loss of pain sensitivity with partial preservation of other types of sensitivity and consciousness. But after anaesthesia, a patient develops amnesia on events taking place during this period.

The stage of excitement lasts 10–20 minutes. This stage is the result of the reduction of inhibitory control of cortical centres over the subcortical centres of brain ("riot" of subcortex). The manifestations of this stage are motor and verbal agitation, loss of consciousness, increased muscular activity, nonstable blood pressure, tachypnoea, and hyperventilation. Due to irritative activity of ether, cough, laryngeal spasm, hypersecretion of salivary and bronchial gland, nausea, and vomiting can occur. Apnea and a sudden cardiac arrest can develop owing to irritation of upper respiratory tract. These effects are prevented by atropine administration. The pupils are dilating.

The stage of surgical anaesthesia is characterized by a loss of consciousness and pain sensitivity, inhibited reflexes, regular respiration, and stabilization of the blood pressure. Diethyl ether well relaxes the skeletal muscles and potentiates the action of curare-like agents.

At ether overdose, the stage of respiratory paralysis develops. This stage is characterized by severe depression of the vital medullary centres that leads to progressive decrease of the blood pressure and respiration, and cardiac arrest. It is clear, that the deepening of the anaesthesia up to this stage is inadmissible.

Diethyl ether activates the central links of sympathoadrenal system that leads to the release of adrenaline from the adrenal medulla. The drug inhibits the renal function. But as a rule, renal function normalizes itself in post-operative period.

In case of deep anaesthesia, the acidosis develops.

Recovery after ether anaesthesia develops gradually (for 30 minutes). The full restoration of brain activity needs several hours. An analgesia is typical for post-anaesthetic period. Also, vomiting is possible during recovery period.

Diethyl ether has insignificant influence upon cardiovascular system. It is due to the direct inhibitory action of ether upon the heart

and vasculature and simultaneous stimulative action upon sympathoadrenal system.

Hepatotoxicity of diethyl ether is low and is dangerous for patients suffering from hepatic diseases. In other patients, ether can cause functional hepatic disorders which disappear in 5–7 days after anaesthesia.

In post-operative period, an elevation of glucose, lactic and pyruvic acids, and acidosis are observed.

Disadvantages of diethyl ether are the marked stage of excitement and expressed irritation of mucous membranes of respiratory tract. The last one leads to laryngeal and bronchial spasm choking feeling and increased bronchial secretion. An irritation of mucous membranes of stomach can provoke the vomiting.

Halothane has high anaesthetic activity that is 3–4 times higher than the activity of diethyl ether. An anaesthesia develops in 3–5 minutes after the start of halothane inhalation. The stage of excitement is insignificant or absent. Halothane does not irritate mucous membranes, does not stimulate bronchial secretion, and does not cause laryngeal spasm. Halothane anaesthesia is easily manageable. After the stop of halothane inhalation, patient recovers in 5–10 minutes. As a rule, afteraction is absent. Halothane anaesthesia is accompanied by satisfactory muscular relaxation. The drug potentiates the effect of curare-like agents. Despite halothane inhibit the respiratory centre in certain degree, this effect quickly disappears after cessation of halothane inhalation.

Halothane suppresses the force of cardiac contraction, reduces the stroke volume and cardiac output, and lowers the blood pressure. Hypotension is a result of direct myotropic antispasmodic action of halothane, reduction of cardiac output, and inhibition of vasomotor centre and sympathetic ganglia.

Halothane increases the sensitivity of the heart to adrenaline that can cause the arrhythmias and even ventricular fibrillation. Therefore, administration of adrenaline, noradrenaline, and ephedrine is contraindicated at halothane anaesthesia. If it is necessary to increase the blood pressure, mesatone is administered.

Halothane inhibits salivary, bronchial, and gastrointestinal secretion. Dispite the fact that halothane insignificantly influences hepatic function, it is contraindicated to patients with hepatic diseases. Halothane slightly reduces renal blood circulation and urination. These changes disappear after the cessation of anaesthesia. Unlike diethyl ether, halothane is non-inflammable agent.

Nitrous oxide provides almost immediate development of anaesthesia. As a rule, the stage of excitement is absent. Nitrous oxide does not exhibit irritative action and does not have negative influence upon parenchymatous organs. After-anaestitic period is characterized by a very fast recovery. Nitrous oxide has low anaesthtic activity and does not cause necessary muscular relaxation. For a necessary depth of anaesthesia, the high contration of nitrous oxide is necessary in inhaled air (about 95 %). A use of such concentration is impossible because it is accompanied by expressed hypoxia (concentration of oxygen is only 5 %). As a rule, the mixture, containing 80 % of nitrous oxide and 20 % of oxygen, is used in anaesthesiology. Such combination provides an opportunity to achieve the initial plane of surgical anaesthesia. To increase the depth of anaesthesia and relaxation of skeletal muscles, nitrous oxide is used in combination with potent anaesthetics (diethyl ether, halothane, barbituric acid derivatives, etc.) and myorelaxants.

Besides inhalational anaesthesia, nitrous oxide is used to relieve pain at myocardial infarction, traumas, parturition, and in postoperative period. The early use of nitrous oxide prevents the shock development in patients with severe traumas. It should be noticed that long-time inhalation (more than a day) of nitrous oxide can lead to leukopenia, megaloblastic anaemia, thrombocytopenia, and neutropenia.

Drugs for Non-Inhalation Anaesthesia

As a rule, drugs for non-inhalation anaesthesia are administered parenterally, sometimes – enterally. In comparison with inhalational anaesthetics, these drugs have some advantages, because provide high speed of anaesthesia development without stage of excitement, do not

require the special anaesthesia-respiratory apparatus, do not induce vomiting, etc.

Non-inhalation anaesthetics are classified as follows:

1. Drugs with short duration of action (duration of anaesthesia is about 15 minutes): *propanidid (sombrevin)* and *ketamine (ketalar)*.

2. Drugs with intermediate duration of action (20–30 minutes): barbituric acid derivatives *thiopental sodium* and *hexenalum (hexobarbital)*;

3. Drugs with long duration of action (60 minutes and more): *sodium oxybutyrate (oxybate sodium)*.

Propanidid (*sombrevin*) is intravenous anaesthetic with ultrashort duration of action. After intravenous administration of the drug, anaesthesia develops in 20–40 seconds without stage of excitement and lasts 4–8 minutes. A short duration of action is due to the fast hydrolysis of the drug by butyrylcholinesterase (also known as pseudocholinesterase). After anaesthesia, the inhibition of central nervous system activity does not appear. Before anaesthesia, the hyperventilation of lungs with short-time apnoe is possible with the following normalization of breath. Minor tachycardia and increase of blood pressure are possible during anaesthesia. Propanidid exhibits a local irritative effect that can cause hyperemia and pain in the veins. Also, formation of clots is possible. Propanidid is used for the induction anaesthesia and for short-term operations.

Ketamine (ketalar) is antagonist of NMDA (N-methyl-D-aspartate) receptors. Ketamine is administered intravenously or intramuscularly. Anaesthesia develops in 30–60 seconds if the drug is administered intravenously, and in 2–6 minutes – in case of intramuscular administration. The duration of ketamine's anaesthesia is about 5–15 minutes (intravenous administration) and 15–30 minutes (intramuscular administration).

The drug causes the so-called "dissociative anaesthesia" because ketamine inhibits some structures of the central nervous system without influence upon others. Ketamine does not directly inhibit the functions of cortex and brainstem; their changes have a secondary

character. Dissociative anaesthesia is characterized by amnesia, expressed analgesia, slight hypnotic effect, and partial loss of consciousness. The drug does not provide muscular relaxation, pharyngeal and cough reflexes are saved. Ketamine increases the blood pressure, heart rate, and intracranial pressure. Hypersalivation is also possible. Ketamine exhibits the moderate broncholytic effect. Ketamine commonly causes hallucinations, disorientation, agitation, and vivid dreams during recovery. The drug is used for induction anaesthesia or for maintenance of anaesthesia during short-term operations or painful procedures (e. g., bronchoscopy, dressing of burns, abortions). In combination with tranquilazers or neuroleptics, ketamine may be used for long-time anaesthesia.

Currently, the clinical use of ketamine in psychiatry is being widely studied. Thus, the drug can be used in the treatment of depression and post-traumatic stress disorder. In addition, ketamine may be useful in the treatment of acute and chronic pain.

Thiopental sodium administered intravenously causes the fast anaesthesia without stage of excitement. Anaesthesia lasts 20–30 minutes. The short duration of anaesthesia is the result of the drug redistribution due to high solubility of thiopental in lipids. Analgesia is poorly expressed. Thiopental sodium is a potent respiratory depressant: both frequency and depth of breathing movements are reduced. Thiopental sodium inhibits the vasomotor centre and cardiac output and decreases the blood pressure. A fast drug administration can lead to collapse. Thiopental sodium exhibits the local irritative effect. Thiopental sodium is used for induction anaesthesia, for anaesthesia during short operations. Also, thiopental may be used to cessate convulsions.

Pharmacological properties of *hexobarbital (hexenalum)* are similar to properties of thiopental sodium. But it should be noticed that hexenalum has more expressed cardiodepressive effect and provokes convulsions more frequently. The indications for use of hexenalum are identical to thiopental.

Sodium oxybutyrate is GABA derivative. The drug easily penetrates the central nervous system. Sodium oxybutirate exhibits

sedative, hypnotic, antihypoxic, narcotic, and anticonvulsive effects. The analgesic action of sodium oxybutyrate is low. The drug causes expressed relaxation of skeletal muscles, increases the resistance of brain and heart to hypoxia. The anaesthetic effect of sodium oxybutirate is moderate. Therefore, for general anaesthesia, the sodium oxybutyrate is administered in high doses. The anaesthesia develops without the stage of excitement. At intravenous administration, the stage of surgical anaesthesia develops in 30–40 minutes; in case of peroral intake – in 40–60 minutes. The anaesthesia lasts 1–3 hours.

The drug administration is accompanied by the minor decrease of frequency and simultaneous increase of depth of breathing. The bradycardia and insignificant increase of the blood pressure are commonly observed. Also, vomiting is possible.

In combination with active analgesics and other general anaesthetics, sodium oxybutyrate is used for introduction and basic anaesthesia, for analgesia of parturition, in the treatment for hypoxic brain oedema and shock. Also, the drug is used as sedative and hypnotic agent.

Preanesthetic Medication

Preanesthetic medication is the term applied to the use of drugs before the administration of general anaesthetics. Preanesthetic drugs are used for the following aims:

– to sedate a patient and reduce fear;

– to prevent such side effects of general anaesthetics as cardiac arrest, vomiting, bronchospasm, hypersalivation, and hypersecretion of bronchial glands;

– to provide rapid onset of anaesthesia without stage of excitement;

– to decrease pre- and postoperative pain.

As preanesthetic agents, the following groups and drugs are used: opioid analgesics (morphine, etc.), tranquilizers (diazepam, etc), M-cholinergic antagonists (atropine and scopolamine), and antiemetic agents (metoclopramide, etc.).

Table 13 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Propanididum	Intravenously 0.005–0.01 g/kg	Ampoules 10 ml of 5 % solution
Hexenalum	Intravenously 0.5–0.7 g	Vials 1.0 g of powder for injection (dissolved before administration in 50 ml of sterile 0.9 % sodium chloride solution)
Thiopentalum-natrium	Intravenously 0.4–0.5 g	Vials 0.5 g or 1.0 g of powder for injection (dissolved before administration in 50 ml of sterile 0.9 % sodium chloride solution)
Natrii oxybutyras	Intravenously 0.07–0.12 g/kg; orally 0.1–0.2 g/kg (for general anaesthesia); orally 2–3 table spoons before bedtime (to treat insomnia)	Ampoules 10 ml of 20 % solution; vials 400 ml of 5 % syrup
Ketaminum	Intramuscularly 0.006 g/kg or intravenously 0.002 g/kg	Vials 20 ml of 5 % solution; ampoules 2.5 and 5 ml of 5 % solution

Step 1. Tasks for Self-Control
General Anaesthetics

1. Proserinum in case of systemic administration increases the tone of skeletal muscles. Phthorothanum (fluothane, halothane) causes relaxation of skeletal muscles and decreases the effects of proserinum. Point out the character of interaction with proserinum and phthorothanum.

A. Noncompetitive antagonism.

B. Indirect functional antagonism.

C. Direct functional antagonism.

D. Competitive antagonism.

E. Independent antagonism.

2. An anaesthesiologist has used nitrous oxide as general anaesthetic during operation. This drug has significant solubility in lipids. Indicate the mechanism of penetration of this drug through biological membranes.

A. Pinocytosis.

B. Active transport.

C. Passive diffusion.

D. Simplified diffusion.

E. Filtration.

3. To anaesthetize the manipulation related to the burn surface treatment, a drug for short-acting narcosis was intravenously injected to a patient. A minute later, blood pressure increased, tachycardia appeared, the tone of skeletal muscles increased; reflexes remained. After awakening, the patient had disorientation and visual hallucinations. What drug was injected to the patient?

A. Ketamine.

B. Nitrous oxide.

C. Sombrevin.

D. Diethyl ether.

E. Thiopental sodium.

4. Proserinum raises skeletal muscle tone when given systematically. Halothane induces relaxation of skeletal muscles and reduces proserinum effects. What is the nature of proserinum and halothane interaction?

A. Indirect functional antagonism.

B. Noncompetitive antagonism.

C. Independent antagonism.

D. Competitive antagonism.

E. Direct functional antagonism.

5. For initial anaesthesia, an anaesthesiologist administers thiopenthal sodium to a patient. Owing to this, hypersalivation and

laryngospasm are developed in the patient. Which drug can prevent these complications?

A. Salbutamol.

B. Adrenaline.

C. Proserinum.

D. Atropine.

E. Ephedrine.

6. For general anaesthesia, an anaesthesiologist uses a combination of inhaled anaesthetic and derivative of barbituric acid. Choose this combination.

A. Droperidol and ether.

B. Promedol and halothane.

C. Nitrous oxide and ketamine.

D. Halothane and fentanyl.

E. Thiopental sodium and halothane.

7. Acute hepatitis developed in a patient after surgery with repeated use of sorting general anaesthetic. Which anaesthetic drug is used?

A. Ether.

B. Halothane (phthorothanum).

C. Nitrous oxide.

D. Thiopental sodium.

E. Propanidid.

8. Anaesthesiologist administers general anaesthetic with prolonged phase of excitation to a patient. Which drug is administered?

A. Oxybutyrate sodium.

B. Phthorothanum (halothane).

C. Ether.

D. Nitrous oxide.

E. Propanidid.

9. Progressive drop of blood pressure is developed in a patient under the general anaesthesia. Doctor administers the injection of adrenaline to him. Owing to this, ventricular fibrillation is developed

in the patient. Indicate the general anaesthetic which is used for narcosis in this case.

A. Ketamine.
B. Nitrous oxide.
C. Sodium oxybutyrate.
D. Sodium thiopental.
E. Phthorothanum.

Hypnotic Drugs

Sleep is an active process developing due to increase of activity of brain hypnotic system (lower parts of the cerebral trunk, basal nuclei of the forebrain, lateral prethalamic and medial thalamic areas, and caudate nucleus). The activity of stimulating the ascending part of the reticular formation (rostral part of reticular formation) during sleep is decreased. The changes in the balance of mediators that lead to sleep are not completely clear.

Sleep is not a uniform process. It includes 2–4 cycles consisting of synchronized or non-REM (REM – rapid eye movement) sleep and desynchronized (REM sleep) phases.

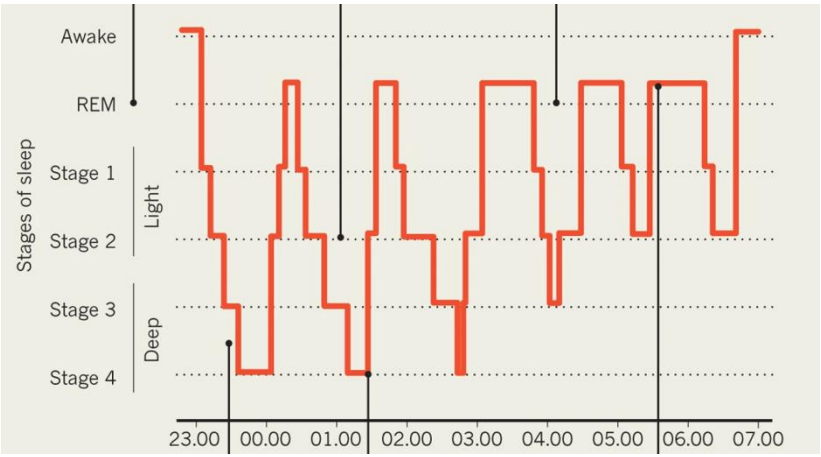

Figure 8 – The sleep architecture

The synchronized sleep consists of four stages with different depths of sleep and EEG (electroencephalogram) characteristics: I stage (transition from a state of vivacity to drowsiness), II stage (drowsiness), III stage (superficial sleep), and IV stage (deep sleep). A phase of synchronized sleep lasts about 1.5 hours. Generally, the phase of synchronized sleep constitutes about 75 % of the sleeping time. During this phase, metabolism slows down, body temperature reduces, blood pressure decreases, and vagal tone elevates. The deficit of synchronized sleep causes the feeling of chronic tiredness, alarm, and decrease of mental performance.

Desynchronized sleep is characterized by low voltage activity on the EEG. This phase is accompanied by quick eye movements and dreams. The duration of desynchronized sleep is approximately 25 % of the sleeping time. The deficit of desynchronized sleep leads to a significant change of psyche and behaviour, and hallucinations.

Sleep disorders require non-pharmacological or pharmacological treatment. Non-pharmacological therapies that are sometimes useful for sleep disorders include proper diet and exercises, avoiding stimulants before retiring to bed, ensuring a comfortable sleeping environment, and retiring at the usual time every night. However, sometimes patients need a sedative-hypnotic agent during the limited period.

Hypnotic drugs are classified as follows:

1. Barbituric acid derivatives: *phenobarbital* and *cyclobarbital*.
2. Benzodiazepine derivatives: *nitrazepam, nozepam (oxazepam), phenazepam, diazepam, lorasepam, flurazepam, temazepam*, and *triazolam*.
3. GABA derivatives: *sodium oxybutyrate* and *phenibut*.
4. Aliphatic compounds: *chloral hydrate* and *bromisoval*.
5. Cyclopyrolone derivatives: *zopiclone (Imovane).*
6. Imidazopyridine derivatives: *zolpidem (Ivadal).*
7. Ethanolamine derivative: *doxylamine (Donormyl).*
8. Melatonin receptor agonists: *melatonin* (*melaxen), ramelteon*.

Besides, drugs of other pharmacological groups are used to treat insomnia: small doses of neuroleptics, antidepressants with sedative effects, sedative drugs and antihistamines.

It should be noticed that only two drugs – sodium oxybutirate and chloral hydrate – induce sleep that is close to the physiological one.

There are three forms of sleep disorders.

Neurastenia or overwork can provoke the disturbances of falling asleep, especially in young people. To fall asleep, a patient needs several hours, after that the deep and long enough sleep develops. For treatmernt of this disorder, hypnotic drugs with short or moderate duration of action are preferable.

Significant part of patients suffers from both disturbances of falling asleep and, in general, disturbances of depth and duration of sleep. Their superficial sleep is characterized by frequent awakenings. A ratio of synchronized and desynchronized sleep changes in favor of the latter. Such patients need hypnotic drugs with long duration of action.

For aged people with atherosclerosis of cerebral vessels, short-time sleep (2–5 hours) with disturbances of falling asleep is typical. Hypnotic drugs with short action (at the time of nightly awakening) or long-acting drugs in the evening are recommended for these patients.

Barbituric Acid Derivatives

Barbiturates bind to barbiturate receptors modulating an activity of $GABA_A$-receptors. It leads to the increase of inhibitory inflence of GABA in the central nervous system. Besides, barbiturates suppress the action of excitatory mediators (glutamic and aspartic acids). Hypnotic effect of barbiturates develops due to inhibition of ascending reticular activating system of the brainstem. It results in the decrease of the tonic pulses to the cortex and development of sleep.

Barbiturates decrease the latency of sleep onset (time to fall asleep) and increase the total duration of sleep. Under barbirurate influence, the duration of stages 2 and 3 of synchronized sleep is increased. But drugs decrease duration of stages 1 (superficial sleep) and 4 (deep, slow-wave sleep) of non-REM sleep. It should be noticed

that barbiturates significantly decrease duration of desynchronized sleep. Hypnotic effect develops in 30–40 minutes after a drug intake and lasts 6–8 hours.

Due to such peculiarities of action, barbiturates are prescribed to treat sleep disordes with prevalence of desynchronized sleep. Cyclobarbital may be prescribed to treat disturbances of falling asleep, because the drug has short duration of action (4–6 hours).

Duration of drug action is determinated by different factors, foremost – by microsomal oxidation in the liver. Barbiturates induce microsomal enzymes that lead to elevation of speed of their biotransformation at repeated intakes.

Duration of drug action also depends on the speed of its excretion from the kidneys, its redistribution in an organism. Material cumulation is typical for lipophilic drugs accumulated in the fat tissue. The half-life of phenobarbital in humans is 4–5 days. This drug is characterized by the most expressed material cumulation.

The disadvantages of barbiturates are the following:

1. Narrow therapeutic index: drug doses which 5–10 times exceed therapeutic doses cause expressed intoxication symptoms, such as a state of general anaesthesia.

2. Alteration of sleep structure with severe syndrome of “REM rebound” after discontinuation of drug intake. “REM rebound” syndrome is characterized by a significant increase of general duration of desynchronized sleep. Vegetative and humoral functions of the body, that increased during desynchronized sleep, increase the risk of myocardial infarction and insult.

3. Fast development of drug dependence accompanied by severe psychical and physical disordes (abstinence syndrome): anxiety, irritability, fear, vomiting, sleep disorders, vision disorders, convulsions, postural hypotension, etc. The addiction to barbiturates can develop after 1–3 months of the barbiturate intake.

4. Tolerance is the result of barbiturates ability to induce the microsomal hepatic system. Tolerance develops after 2 weeks of regular barbiturate intake.

5. A phenomenon of after-action (flaccidity, weakness, disturbance of psychomotor reactions and attention) is observed even after a single intake of long-action barbiturates. The slower the drug is excreted, the greater the aftereffects. Also, small doses of barbiturates (1/2–1/3 of a hypnotic dose) exhibit sedative effect. High doses of barbiturates act as anticonvulsants.

Barbiturate overdose leads to general depression of the central nervous system, reduction of pulmonary ventilation, and drop of blood pressure. Severe intoxication results in coma. Hypotension is due to the inhibition of vasomotor centre in medulla oblongata, drug influence upon the heart and sympathetic ganglia, and direct vasodilating action of drugs. Besides, barbiturates violate renal function.

A treatment of poisoning by barbiturates includes the following measures:

1. Increase of barbiturate elimination from the body: gastric lavage, forced diuresis (administration of significant volumes of electrolytes solutions together with osmotic diuretics or furosemide), administration of alkaline solutions (intravenous sodium hydrocarbonate solution), saline laxatives, and hemodialysis.

2. Restoration of pulmonary ventilation and blood circulation.

3. Administration of antidote. Bemegride is analeptic drug. But its administration is possible only at the light form of poisoning, because at severe poisoning the drug can even aggravate the patient's condition. In any cases, an artificial ventilation is the most reliable method to support breathing.

4. Plasma-substitution drugs and noradrenaline are administered at collapse.

5. At renal failure, hemodialysis is fulfilled.

It should be noticed that pneumonia is possible at barbiturate poisoning.

Chronic poisoning commonly develops due to the intake of drugs with a high ability to cumulation. Chronic poisoning is manifested by drowsiness, apathy, weekness, imbalance, indistinct speech, and

dizziness. Halucinations, psychomotor excitement, convulsions, renal and hepatic disfunction, and indigestion are also possible.

At barbiturate dependence, the dose of the drug is gradually reduced up to the full discontinuation of a drug intake. Simultaneously, symptomatic treatment and psychotherapy are carried out.

Benzodiazepine Derivatives

Benzodiazepine derivatives exhibit anticonvulsant, hypnotic, anxiolytic effects. These drugs are highly effective in patients with insomnia due to neurotic disorders. Unlike barbiturates, benzodiazepine derivatives change a sleep structure in less degree.

As hypnotic agents, benzodiazepines with moderate duration of action (nitrazepam, lorazepam, nozepam, triazolam, flunitrazepam) and with long duration of action (diazepam, chlozepid, fenazepam, flurazepam) are used most commonly.

Hypnotic effect of benzodiazepines is mediated by their influence upon limbic system. Benzodiazepine interacts with a specific benzodiazepine receptor which is the part of $GABA_A$-chloride channel macromolecular complex. This interaction leads to the increase of sensitivity of $GABA_A$-receptors to GABA. Activatated $GABA_A$-receptors cause the opening of chlorine channel. Chlorine ions enter the cell that leads to hyperpolarization of a cellular membrane. It reduces the neuronal activity. Besides, benzodiazepines promote the elevation of GABA concentration in the brain. This effect develops due to inhibition of GABA-transaminase. Along with serotonin and delta-sleep-inducing peptide, GABA is responsible for the development of synchronized sleep.

Benzodiazepines cause the following changes in the sleep structure:

– the latent period of sleep onset is shortened (time to fall asleep);

– the duration of stage 2 of synchronized sleep is increased;

– the duration of REM sleep is decreased;

– the duration of stage 4 of non-REM sleep is decreased. More rapid onset of sleep and prolongation of stage 2 are clinically useful effects.

After a drug intake, hypnotic effect develops in 20–30 minutes and lasts 6–8 hours (midazolam – 2–4 hours).

Benzodiazepines are used to treat disorders of falling asleep and other forms of insomnia. These drugs are especially active as hypnotics in patients with emotional tension, anxiety, and alarm. Nitrazepam, temazepam, and flurasepam are used only as hypnotics. Other benzodiazepines are used more widely in medicine.

The phenomenon of after-action (flaccidity, weakness, disturbance of psychomotor reactions and attention) is observed during the next day, especially after the intake of long-acting benzodiazepines. Therefore, benzodiazepines are not prescribed for persons whose work needs high attention.

Midazolam is preferable at the night awakenings and disorders of falling asleep. Also, this drug is prescribed in cases when a long-time therapy of insomnia is needed.

A long-time therapy with benzodiazepines leads to the development of tolerance, drug dependence, and rebound syndrome. Ethyl alcohol significantly increases the depressive influence of these drugs upon the central nervous system that can cause respiratory failure.

Flumazenil (*Romazicon*) is a competitive antagonist of benzodiazepine receptors. This drug is used to stop the toxic effects at overodse of benzodiazepines.

GABA Derivatives

Sodium oxybutyrate is a GABA derivative and is known as general anaesthetic. This drug also has a hypnotic action. Sodium oxybutyrate prolongates the duration of a deep stage of the synchronized sleep without significant influence upon the desynchronized sleep. After a drug removal, rebound syndrome is mild and significantly less than in barbiturate derivatives. Sodium oxybutyrate does not cause the phenomenon of after-action. As hypnotic agent, sodium oxybutyrate is prescribed in 5 % syrup (2–3 tablespoons before bedtime). The hypnotic effect develops in 30–40 minutes after the drug intake and lasts 6–8 hours.

Phenibut is an agonist of $GABA_B$-receptors. The drug has low hypnotic activity. Phenibut is used mainly as "daily" tranquilizer. Phenibut does not influence the sleep structure.

Aliphatic Compounds

As hypnotic, *chloral hydrate* is administered as rectal solution together with covering substances (because the drug has a marked local irritative action). A sleep develops in 30–60 minutes after the drug administration and lasts 6–8 hours. Phenomenon of after-action is typical for chloral hydrate. Besides, chloral hydrate exhibits hepato-, nephro-, and cardiotoxicity.

Another hypnotic agent – aliphatic compound is *bromisoval*. Its hypnotic effect is low and non-stable.

Both drugs are seldom used to treat insomnia.

Non-Benzodiazepine Compounds – Agonists of Benzodiazepine receptors

Z*opiclone* and *zolpidem* are non-benzodiazepine compounds which exhibit the affinity to benzodiazepine receptors. These drugs bind to BZ_1 subtype of benzodiazepine receptors that facilitates the activation of $GABA_A$-receptors by GABA, opening of chlorine channes, and hyperpolarization of a cellular membrane.

Zopiclone is a cyclopyrrolone derivative. Besides hypnotic action, the drug exhibits sedative, anticonvulsant, anxiolytic, and amnestic actions. Also, zopiclone is a central myorelaxant. The drug shortens the time of feeling asleep, decreases the quantity of night awakenings, and increases the total duration of a sleep. A phenomenon of after-action is absent. Zopiclone is not accumulated in the body. A course of treatment by zopiclone should not exceed 4 weeks. Its side effects are nausea, vomiting, headache, dizziness, allergic reactions, halucinations, discoordination, and nightmares. Rebound syndrome is insignificant.

Zolpidem is imidazopyridine derivative. The drug selectively interacts with BZ_1 subtype of benzodiazepine receptors. The drug exhibits hypnotic, sedative, anxiolytic, muscular-relaxating,

anticonvulsant, and amnestic action. Zolpidem is easily absorbed from the gastrointestinal tract. Its bioavailability is about 70 %. The 2/3 parts of an administered dose is excreted through the kidneys and 1/3 – through the intestine. Side effects of zolpidem are allergic reactions, hypotension, excitation, halucinations, dispepsy, daily drowsiness, and headache.

Flumazenil is antagonist of zolpidem and zopicline.

Ethanolamine Derivatives

Doxylamine (*Donormyl*) is ethanolamine derivative. The drug blocks H_1-histaminergic and M-cholienrgic receptors. Donormyl exhibits hypnotic, sedative, antiallergic, and peripheral M-cholinoblocking activity. Donormyl shortens the time of falling asleep, increase the duration of sleep, does not violate the sleep structure, and does not exhibit after-action. Donormyl is used to treat insomnia, allergic diseases, cough, and colds. Its side effects are a dry mouth, constipation, disorders of accommodation, difficulty urinating, etc. The drug is contraindicated to persons whose work needs high attention.

Melatonin Receptor Agonists

M*elatonin* (*melaxen)* is a preparation of a native human hormone secreted by the pineal gland of the brain. Its secretion increases in the dark. Melatonin is an agonist of MT_1- and MT_2-melatonin receptors. These receptors are involved in the regulation of sleep-wake cycles. The drug is taken orally at night in a dose of 0.003–0.005 g. There is evidence, that melatonin is also involved in the regulation of mood, memory, immune activity, and other physiological processes of the body.

Ramelteon is a synthetic analogue of melatonin approved for use in 2005. Its efficacy is higher than that of melaxen. The drug is used to treat insomnia with difficult onset of sleep. Ramelteon is taken orally within 30 minutes of going to bed at a dose of 8 mg. The drug may be used for the long-time treatment of insomnia because drug dependence and tolerance are not typical for ramelteon. Besides,

discontinuation of the drug intake does not provoke “REM rebound” syndrome. Side effects of ramelteon are daytime drowsiness, dizziness, headache, and allergic reactions.

Ethyl Alcohol

Ethanol is substance with narcotic type of action. Ethyl alcohol causes the total depression of the central nervous system. At local application, ethanol causes denaturation and dehydration of proteins (including proteins of cellular membranes), that is the base of its antiseptic action. This effect is used to disinfect skin and surgeon’s hands, and to sterilize instruments.

It should be noticed that 70 % ethyl alcohol provides maximal antibacterial effect at skin disinfection. Higher concentrations of ethanol exhibit less expressed antibacterial effect because fast protein denaturation on the skin surface prevents ethanol penetration to deep layers of skin. 90–95 % ethanol is used to sterilize instruments.

40 % ethanol exhibits local irritative action, whereby is used for compresses and rubbing. Also, ethanol is used to preserve the preparations of tissues and organs, as solvent and as extractant for preparation of tinctures and liquid extracts.

At oral intake, ethanol increases the secretory activity of the mucous membranes of mouth and stomach due to its irritative action. Gastric secretion and digestibility of gastric juice depend on ethanol concentration. Thus, low concentration of ethanol (to 10 %) stimulates gastric secretion. Ethanol concentration, that is higher than 20 %, inhibits production of pepsin and reduces digestibility of gastric juice. In case of chronic alcohol consumption, it can cause the development of chronic gastritis.

Ethyl alcohol is absorbed both in stomach and in intestine. 10–20 % ethanol is absorbed quickly, but absorption of concentrated ethanol solutions is slow and lasts 2–6 hours. Sometimes, concentrated ethanol solution causes pylorospasm.

Ethyl alcohol easily penetrates through the blood-brain and placentar barriers. Children, born by mothers who abuse alcohol, often are mentally underdeveloped.

About 90 % of taken alcohol undergoes hepatic oxidation by alcohol dehydrogenase with formation of acetaldehyde. The subsequent metabolism of acetaldehyde is very slow. Therefore, accumulation of acetaldehyde causes the development of marked intosixation (handover): headache, disorders of heart work, etc. Metabolism of ethanol is slowed in persons with hepatic diseases.

Long-time intake of ethyl alcohol leads to expressed psychical disorders (delirium tremens).

Ethyl alcohol has a high energetic value (7 kcal are released at burning of 1 g of ethanol). This property is sometimes used in the treatment for patients with fever when body proteins are catabolized. Also, ethanol is used in the treatment of depleted patients (after operations on gastrointestinal tract, at prolonged vomiting, etc.). In such cases, a small amount of ethyl alcohol is added to solutions for intravenous infusions.

Ethanol significantly influences thermoregulation, increasing both a heat production and a heat emission.

Ethanol decreases the vasopressin release by posterior pituitary that leads to the increase of diuresis.

Ethanol exhibits mainly inhibitory influence upon the central nervous system. There are four stages of its influence upon CNS: analgesia, excitement, general anaesthesia, and agony. Most commonly, alcoholic intoxication is manifested by excitation developed due to the reduction of inhibitory processes in the central nervous system. It is accompanied by loss of critical attitude to own actions and people around. High doses of ethanol directly inhibit the brain cortex.

Narrow therapeutic index and marked stage of excitement do not allow to use ethanol as general anaesthetic. But, ethyl alcohol sometimes may be used as anti-shock agent owing to its marked analgesic property.

Ethanol is used in medical practice as follows:

– antiseptic agent: 95 % ethanol – for disinfection of medical instruments and 70 % ethanol – for disinfection of surgeon’s hands and skin;

– for compress – 40 % ethanol;

– foam-extinguisher for treatment of pulmonary oedema: ethanol is used for inhalation, or 20–30 % ethanol in sterile isotonic solution of sodium chloride is administered intravenously;

– for treatment of methanol's poisoning (orally 300–400 ml 30 % ethanol per day or 5 % ethanol intravenously drop-by-drop in dose which equals 1ml per 1 kg of weight of a patient per day). In this case ethanol competes with methanol for active centre of enzyme "aldehyde dehydrogenase" and lowers toxic effects of methanol.

Excessive ethanol intake can lead to acute poisoning. The degree of ethanol intoxication depends on its blood concentration: concentration 1–2 g/l causes inebriation, 3–4 g/l – intoxication, and 5–8 g/l – death. Toxic doses of ethanol inhibit vital centres of medulla oblongata. Symptoms of marked poisoning by ethanol are loss of consciousness, pale skin, hypothermia, relaxation of skeletal muscles, reduction of perspiration, inhibition of the heart work. Paralysis of respiratory centre leads to death.

A treatment of acute poisoning by ethanol includes the following measures:

– cleaning of oral cavity and upper respiratory ways;

– atropine administration for reduction of hypersecretion of salivary and bronchial glands;

– inhaled oxygen;

– artificial respiration;

– administration of analeptics (cordiamine, caffeine, etc.);

– gastric lavage;

– intravenous administration of sodium hydrocarbonate for correction of acid-base balance;

– administration of antiemetic drugs (metoclopramide, etc.)

– hemodialysis at severe alcohol poisoning.

Poisoned patient should be in a heated room because ethanol affects thermoregulation.

Chronic poisoning by ethanol (alcoholism) is characterized by significant changes of higher nervous activity, irritability, disorders of sleep and digestion, unstable mood, etc. Mental and physical working

capacity and attention are reduced. Subsequently, alcoholic psychosis and disorders of peripheral nervous system are developed. Alcoholism is accompanied by severe damages of inner organs: chronic gastritis, heart obesity, cirrhosis of the liver, and kidney dystrophy.

Both medicamental therapy and psychotherapy are used in the treatment for alcoholism. *Teturam* (*disulfiram*) is one of the drugs for treatment of chronic alcoholism. It is prescribed together with small amount of ethyl alcohol. Teturam inhibits aldehyde dehydrogenase that leads to accumulation of acetaldehyde in body. Acetaldehyde is highly toxic substance; its accumulation results in the heart pain, fear, headache, hypotension, nausea, vomiting, sweating, choking feeling, etc. A treatment with teturam promotes the formation of negative conditional reflex to ethyl alcohol. The treatment is carried out only for inpatients. Contraindications to teturam are cardiovascular, hepatic, renal, and metabolic diseases. Also, the drug is contraindicated to patients over 50 years of age. There are prolonged teturam-containing preparations (*Esperal*, *Radoter*) for subcutaneous implantation.

Table 14 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
Nitrazepamum	Orally 0.005–0.01 g (before bedtime)	Tablets 0.005 or 0.01 g
Phenobarbital	Orally 0.1 g (before bedtime)	Tablets 0.05 or 0.1 g
Aethaminalum-natrium	Orally 0.1–0.2 g (before bedtime)	Tablets 0.1 g
Zolpidem	Orally 0.01 g (before bedtime)	Tablets 0.01 g
Natrii oxybutiras	Orally 2–3 table spoons (before bedtime)	Vials 400 ml of 5 % syrup
Teturamum	Orally 0.5 g 1 time a day	Tablets 0.25 g

Step 1. Tasks for Self-Control
Hypnotic Drugs. Ethyl Alcohol

1. A female complains of insomnia after psycho-emotional stress. What drug has the advantage for treatment of this patient?

A. Nitrazepam.
B. Barbital.
C. Phenobarbital.
D. Aethaminal sodium (pentobarbital).
E. Barbamil.

2. A patient complains of insomnia due to emotional disturbances. The doctor has prescribed him the hypnotic drug with a tranquilizing action. What drug has been prescribed to the patient?

A. Bromisoval.
B. Nitrazepam.
C. Phenobarbital.
D. Chloral hydrate.
E. Aethaminal sodium.

3. An 18-year-old patient complains of insomnia, which is manifested as difficulty in getting to sleep. As a result, on the next day the patient feels weakness, weariness, and has difficulty in training. The doctor has defined, that the insomnia is connected with neurosis. Make the rational choice of the hypnotic drug.

A. Aethaminal sodium.
B. Nitrazepam.
C. Bromisoval.
D. Chloral hydrate.
E. Phenobarbital.

4. A 17-year-old woman took an overdose of phenobarbital for the suicidal purpose. The urgent doctor made gastric lavage, introduced bemegride and sodium hydrocarbonate solution intravenously. For what purpose has the doctor introduced the sodium hydrocarbonate?

A. For wakening effect.
B. For stimulation of breathing.
C. For normalization of blood pressure.
D. For inactivation of phenobarbital.

E. For increase of kidney excretion of phenobarbital.

5. A 50-year-old female suffers from insomnia. She has used different hypnotic drugs (aethaminal sodium, phenobarbital, and barbamil) during 3 months. After withdrawal of the drugs the woman became irritable, aggressive, the tremor of hands and loss of appetite have appeared. What is the complication, which has developed in a woman, called?

A. Functional cumulation.

B. Tachyphylaxis.

C. Physical and psychic dependence.

D. Sensitization.

E. Tolerance.

6. Prescribe to a patient, complaining of insomnia, a modern soporific which is an imidazopyridine derivative. It influences benzodiazepine receptors in the CNS, does not violate the structure of sleep, does not cause dependence, does not change the activity of liver enzymes. What is it?

A. Phenobarbital.

B. Chloral hydrate.

C. Nitrazepam.

D. Calcium chloride.

E. Zolpidem.

7. The effective hypnotic drug which does not influence the REM sleep is prescribed to a patient with sleeping disorders. Choose this drug.

A. Aminazine.

B. Phenobarbital.

C. Oxybate sodium (oxybutyrate sodium).

D. Zopiclone.

E. Dimedrol.

8. A doctor has introduced intramuscularly caffeine to a young patient in condition of alcohol intoxication. What is the base of expediency of such manipulation?

A. Summation of affects.

B. Physiological antagonism.

C. Synergism.

D. Potentiation.

E. Competitive antagonism.

9. Disulfiram is widely used in medical practice to prevent alcoholism. It inhibits aldehyde dehydrogenase. An increased level of what metabolite causes the aversion to alcohol?

A. Ethanol.

B. Methanol.

C. Acetaldehyde.

D. Propionic aldehyde.

E. Malonyl aldehyde.

Opioid Analgesics

This group includes agents of natural, semisynthetic, and synthetic origin which influence central nervous system and exert marked analgesic activity. A prolonged use of these drugs leads to the development of psychical and physical dependence. All effects of these drugs are due to their interaction with opioid receptors. On the base of their interaction with opioid receptors, these drugs are classified as follows:

1. Agonists of opioid receptors:

1.1. Drugs of natural origin: *morphine, codeine,* and *omnopon.*

1.2. Semisynthetic and synthetic drugs: *ethylmorphine hydrochloride, meperidine, promedol (trimeperidine), fentanyl, sufentanil, piritramide,* and *tramadol.*

2. Agonists-antagonists and partial agonists of opioid receptors: *pentazocine, nalorphine, buprenorphine,* and *butorphanol.*

Opium is a withered milky juice derived from unripe seed pots of opium poppy.

Figure 9 – Opium poppy (*Papaver somniferum*)

Opium contains about 20 alkaloids. The main among them is morphine; its concentration in opium is about 10–20 %. Morphine was obtained in a crystal form in 1806. The chemical synthesis of morphine is unprofitable; therefore, nowadays morphine is derived from opium. Besides, pharmaceutical industry produces omnopon, which is the neogalenical opium drug containing about 50% of morphine.

On the base of a chemical structure, alkaloids of opium are divided into two groups: phenanthrene derivatives (morphine, codeine, thebaine, etc.) and isoquinoline derivatives (papaverine, noscapine, etc.). Phenanthrene derivatives exhibit the analgesic and antitussive effects and cause drug dependence. Isoquinoline derivatives exert the antispasmodic action.

Pain is a body reaction upon the harmful stimuli. Pain is perceived by special nociceptors located in the skin, muscles, inner organs, etc. From nociceptors, pain impulses are carried out to the dorsal horn of the spinal cord, where they are transmitted to an intercalative neuron. From the dorsal horn, impulses are carried out to the corresponding arrears of the brain – reticular formation, limbic system, thalamus, and hypothalamus. The final formation of the pain reaction occurs in the cortex. Activation of the limbic system results in a negative emotional reaction upon the pain. Several neurotransmitters participate in transduction of pain: dopamine, serotonin, substance P, somatostatin, and cholecystokinin.

In a human organism, the formation of pain reaction is also under control of a so-called antinociceptive system. The antinociceptive system includes opioid receptors of the CNS, descending tracts, intercalative neurons, and neurons of posterior horns of the spinal cord. The antinociceptive system inhibits the pain transmission mainly by means of endogenous analgesic peptides (enkephalins, endorphins, dynorphins, etc.). These peptides interact with opioid receptors and excite them. Opioid receptors are in the brain areas participating in pain impulses transmission: spinal cord, brainstem, thalamus, hypothalamus, limbic system, hypocampus, and brain cortex.

Opioid receptors are located mainly in presynaptic membranes. Also, these receptors are in postsynaptic membranes outside of the synapses. Presently, three main families of opioid receptors are identified: μ-, δ-, and κ-receptors.

Functional value of opioid receptors is as follows:

– μ_1-receptors inhibit the pain transmission on the supraspinal level; increase the tone of smooth muscles; induce miosis, sedation, euphoria, and psychical dependence;

– μ_2-receptors inhibit respiration and cause physical dependence;

– δ-receptors regulate pain transduction, emotions, activity of vasomotor centre;

– κ-receptors inhibit pain transduction in the spinal cord, cause sedation and drug dependence;

Excessive pain can aggravate the patient's state because it changes the activity of cardiovascular system, tissue perfusion, respiratory function, and immune function. Therefore, pathological states accompanied by excessive pain need an administration of analgesics.

Opioid analgesics interact with opioid receptors. Agonists activate all families of opioid receptors. Agonists-antagonists, as a rule, activate κ-receptors and block μ- and δ-receptors. Antagonists (naloxone and naltrexone) block all families of opioid receptors.

μ-Receptors are associated with adenylyl cyclase. Interaction of opioid agonists with these receptors leads to the decrease of adenylyl cyclase activity and to reduction of intracellular concentration of

cAMP. It leads to the decrease of calcium entry to cells. Simultaneously, activation of opioid receptors leads to potassium efflux and hyperpolarization of neuronal membrane. The net result of excitation of opioid receptors is a decrease in the release of pain mediators and reduction of nociceptive transmission.

The following pharmacological effects are typical for opioid analgesics.

Analgesia. An analgesic action of opioid analgesics is realized maily at the level of gray matter of midbrain and diencephalon. Besides, opioid analgesics inhibit the pain transmission through the gelatinous substance of posterior horn of spinal cord, subcortical structures (thalamus, hypothalamus, hyppocampus, and amygdala), and brain cortex. Thus, analgesic effect is associated by both inhibition of transmission of pain impulses in the central nervous system and violation of emotional perception of pain.

Additionally, opioid analgesics induce euphoria (due to excitation of μ--receptors), reduce fear, anxiety, stress, and mental discomfort. Patients become inattentive to the painful stimuli, less anxious, and more relaxed. In patients who receive opioid analgesic for the first time, marked euphoria develops very seldom. But namely a desire to renew euphoria is the cause of development of psychical and physical dependence to morphin. It should be noticed that such agents as tramadol and pyrithramide cause mild euphoria. Agonists-antagonists (pentazocine, butorphanol, etc.) do not cause euphoria but exert sedative and hypnotic effects. Unlike agonists, drug dependence to these drugs develops slowly and is characterized by a mild withdrawal syndrome.

Sedative and hypnotic effects. Sleep induced by opioid analgesics is accompanied by bright pleasant dreams. Morphine-induced sleep is superficial and is quickly interrupted by any external stimulus.

Inhibition of respiratory centre. Opioid analgesics depress respiration due to excitation of the μ_2-receptors of respiratory centre in medulla oblongata. At therapeutic doses, the slowing of breathing is compensated by its deepening, but in increasing of the dose the reduction of respiratory minute volume up to respiration of Cheyne–

Stokes is observed. The lethal doses of opioid analgesics cause the paralysis of respiratory centre and death of a patient. It should be noticed that a decrease of pulmonary ventilation is insignificant in conscious patients and critically increases in unconscious or sleeping persons.

Antitussive effect. Morphine significantly depresses the cough centre in the medulla oblongata. Less doses of morphine, than those required for analgesia, exhibit an antitussive effect. It should be noticed that inhibition of the cough centre worsens sputum discharge from respiratory ways.

Morphine inhibits vomiting centre in 85–90 % of patients. But in 10–15 % of patients, morphine administration induces nausea and vomiting.

Morphine insignificantly suppresses vasomotor centre that leads to the short-time mild hypotension.

The drug inhibits centre of thermoregulation in hypothalamus.

Morphine increases the tone of vagus nerve. It leads to bradycardia, increases tone of smooth muscles (gastrointestinal tract, uterus, bronchi, biliary and urinary tracts). Besides, morphine exerts direct spasmodic action upon intestine, biliary ducts, and urinary tract. Evacuation of gastric contents is slowed down up to 8–12 hours (instead of 2–4 hours). Under the morphine influence, the tone of gastrointestinal tract and sphincters is increased, but the intestinal motility is decreased. Together with increased water absorption, it leads to constipation.

Morphine increases the vasopressin release by posterior pituitary. It stimulates water absorption from the gastrointestinal tract and decreases diuresis.

Morphine increases bronchial tone and can provoke asthma attacks due to the liberation of histamine and increase of parasympathetic tone.

Morphine causes miosis due to the stimulation of nuclei of oculomotor nerve. This symptom has a high diagnostic value in case of morphine overdose.

Morphine improves coronary blood flow and dilates cerebral vessels. The intracranial pressure is increased. Therefore, at cranial traumas, the administration of morphine is contraindicated.

There is now evidence that opioid receptors (δ- and κ-) are involved in the development of ischemic preconditioning. It is a process in which the repetition of short episodes of cardiac ischaemia leads to increased myocardial resistance to subsequent more severe ischaemic attacks. Agonists of opioid receptors such as morphine and fentanyl have ischemic preconditioning effect and provide cardioprotective action.

Morphine decreases the release of adrenocorticotropin and gonadotropins by anterior pituitary.

Administration of morphine results in hyperglycemia.

Therapeutic doses of morphine do not inhibit spinal reflexes.

After intravenous administration, the effect of morphine develops immediately and lasts to 2 hours. At subcutaneous administration, the effect develops in 15–20 minutes and lasts 4–5 hours. The drug binds with plasma proteins. Morphine undergoes biotransformation in the liver. The metabolites are excreted by kidneys. Insignificant concentration of morphine is excreted by gastrointestinal tract, salivary glands, and mammary glands. It should be noticed that morphine is excreted by gastric glands into the stomach where it undergoes the secondary absorption. Therefore, patients poisoned by morphine need gastric lavage, even if poisoning is due to intravenous morphine administration.

Therapeutic indications for opioid analgesics are as follows:

1. Intensive pain associated with severe traumas, surgical operations, and incurable malignant tumors.

2. Premedication, especially in the heart surgery.

3. Neuroleptanalgesia. Fentanyl is administered together with neuroleptic droperidol. Pharmaceutical industry made a combined drug “Thalamonal” containing 2.5 mg of droperidol and 0.05 mg of fentanyl in 1 ml.

4. Cough threatening to a patient’s life (tuberculosis, tumors, penetrating wounds of chest).

5. Myocardial infarction. Morphine and fentanyl are used most commonly.

6. Biliary and urinary colics and acute pancreatitis. At urinary colic, the promedol (trimeperidine) is a drug of choice. Pentazocine is preferable at biliary colics. It should be noticed that opioid analgesic should be administered together with antispasmodic agent (atropine, platyphyllin, papaverine) to cessate such pathological states.

Opioid analgesics are contraindicated for children under 3 years of age and for elderly (because of the danger of breathing suppression).

Long-time administration of morphine leads to tolerance. In this case, the increased doses should be given for achievement of the necessary effect.

Morphine addiction (chronic poisoning by morphine) develops due to psychical and physical dependence and tolerance. One of the dependence reasons is reduction of synthesis of endogenous enkephalins and endorphins due to chronic morphine administration. The sudden interruption of morphine administration results in acute deficiency of enkephalins and endorphins, the level of which is not compensated by exogenous administration of morphine. In this case, the withdrawal syndrome or abstinence is developed. The symptoms of withdrawal syndrome are aggravation of pain sensitivity, fear, alarm, negative emotions, and vegetative disordes (aberrations of the heart rate, tachycardia, nausea, and anorexia). The abstinence symptoms reduce after the restoration of synthesis of endogenous enkephalins and endorphins.

An acute poisoning by opioid analgesics develops due to their overdose. Main manifestations of acute poisoning are loss of consciousness, increase of spinal reflexes, inhibition of breathing, miosis, gradual decrease of blood pressure, bradycardia, hypothermia, and anuria. In serious cases, coma and breathing of Cheyne–Stokes are observed. The treatment of poisoning includes an administration of antagonists (naloxone or naltrexon), artificial respiration, oxygenotherapy, warming of a patient, atropine sulfate administration, and gastric lavage with 0.05 % potassium permanganate solution.

Promedol (trimeperidine) is phenylpiperidine derivative. Promedol is 2–4 times less active analgesic than morphine. Its duration of action is 3–4 hours. Unlike morphine, promedol is less potent

depressant of the respiratory centre. Promedol has less spasmodic action upon gastrointestinal tract. Unlike morphine, promedol relaxes the smooth muscles of bronchi, of uterus neck, and of urinary tract. Promedol is characterized by low toxicity in children and pregnant women. This agent may be used for analgesia of labor.

Fentanyl is phenylpiperidine derivative with short duration of action. At intravenous administration, the effect of fentanyl develops in 2–3 minutes and lasts 30–40 minutes. The analgesic activity of fentanyl is 100 times more than morphine activity. Fentanyl causes marked inhibition of respiration, sinus bradycardia, rigidity of skeletal muscles of the chest and extremities. Fentanyl can provoke bronchospasm. Fentanyl is used for neuroleptanalgesia, for premedication, for pain relief at myocardial infarction. At chronic pain and in postoperative period, fentanyl-containing transdermal plasters (e. g., Fentavera) are used for analgesia. Their duration of action is about 72 hours.

Phenylpiperidine derivative *pentazocine* is an agonist-antagonist of opioid receptors. This drug is characterized by moderate analgesic activity (3–6 times less than morphine) and by low suppression of the respiratory centre. Pentazocine increases blood pressure and can provoke tachycardia owing to stimulation of sympathetic nervous system. Administration of pentazocine results in reduction of coronary blood flow. Drug poorly penetrates through the placental barrier, therefore, may be used for pain relief of labor. Pentazocine may be used in pediatric practice.

Tramadol is 5–10 times less active analgesic than morphine. Its effect develops quickly and lasts about 9 hours. Therapeutic doses of tramadol do not suppress respiration. The drug has mixed (opioid and non-opioid) mechanism of action. Non-opioid component is associated with reduction of neuronal reuptake of serotonin and noradrenaline that reduces pain transmission. Tramadol is used to treat moderate and severe pain. The drug is taken orally and administered rectally, subcutaneously, intramuscularly, and intravenously.

Phenanthrene derivative *buprenorphine* also is agonist-antagonist of opioid receptors. Analgesic activity of buprenorphine is 20–60 times higher than morphine activity. Its analgesic effect develops slowly. Buprenotphine has less influence upon

gastrointestinal tract than morphine. The drug is taken sublingually or administered parenterally to treat moderate and severe pain. Unlike morphine, buprenorphine seldom causes the development of drug dependence.

Codeine and *ethylmorphine hydrochloride* are used as antitussive agents. Both drugs also exert sedative and analgesic effects. Ophthalmic solution of ethylmorphine hydrochloride dilates vessels and reduces corneal opacity.

Naloxone, nalmefene and *naltrexone* are full antagonists of opioid receptors.

Naloxone and nalmefene are used to treat acute poisoning by opioid analgesics. The agents block opioid receptors and eliminate the main effects of opioid analgesics. Naloxone is administered both intravenously and intramuscularly. The half-life of naloxone is 1 hour. Therefore, in case of opioid overdose, the drug should be administered repeatedly. The duration of action of nalmefene is about 10 hours. The drug is administered intravenously.

Antagonist activity of naltrexone is 3–5 times higher than naloxone activity. Its duration of action is 24–72 hours. It is used orally in the treatment of opioid abstinence.

Table 15 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
1	2	3
Morphini hydrochloridum	Orally 0.01 g; subcutaneously 0.01 g	Powders; ampoules 1 ml of 1 % solution
Omnoponum	Orally 0.01–0.02 g; subcutaneously 0.01–0.02 g	Powders; ampoules 1 ml of 1 or 2 % solution
Promedolum	Orally 0.025 g; subcutaneously 0.01–0.02 g	Tablets 0.025 g; ampoules 1 ml of 1 or 2 % solution
Phentanylum	Intramuscularly or intravenously 0.00005–0.0001 g	Ampoules 2 or 5 ml of 0.005 % solution

Continuation of the table 15

1	2	3
Pentazocini lactas	Subcutaneously or intramuscularly 0.03 g; rectally 0.05 g	Ampoules 1 ml of 3 % solution; suppositories 0.05 g
Pentazocini hydrochloridum	Orally 0.05 g	Tablets 0.05 g
Naloxoni hydrochloridum	Subcutaneously, intramuscularly or intravenously 0.0004–0.0008 g	Ampoules 1 or 2 ml of 0.04 % solution

Step 1. Tasks for Self-Control
Opioid Analgesics

1. A patient with signs of poisoning by morphine was delivered to an emergency department. What drug should be used in this case for gastric lavage?

A. Boric acid.

B. Sodium hydrocarbonate.

C. Potassium permanganate.

D. Nitrofural (furacilinum).

E. Solution of sodium chloride.

2. A patient in a postoperative period received promedol (trimeperidine). Due to the stop of the drug intake, the serious psychical and physical disturbances developed in the patient. What is this complication called?

A. Tolerance.

B. Idiosyncrasy.

C. Tachyphylaxis.

D. Phenomenon of feedback.

E. Abstinence.

3. An unconscious patient was delivered to the hospital. The skin is cold, pupils are narrow, the breathing is complicated and periodic, blood pressure is low, and the bladder is overflowed. What group of drugs is the reason of this poisoning?

A. Neuroleptics.

B. Opioid analgesics.

C. Tranquilizers.

D. Non-opioid analgesics.

E. M-cholinoblockers.

4. Acute spastic pain has developed in a patient with urolithiasis. For prevention of pain shock the doctor has introduced to the patient atropine with opioid analgesic, which does not have spasmogenic action. Call this opioid analgesic.

A. Ethylmorphine hydrochloride.

B. Promedol (trimeperidine).

C. Tramadol.

D. Piritramide.

E. Morphine hydrochloride.

5. A doctor prescribed promedol to a patient with nonresectable tumor of stomach. After some time, the patient has noted the decrease of analgesic action and duration of the drug action. What is the reason of this phenomenon?

A. Decrease of the drug reabsorption in kidneys.

B. Tachyphylaxis.

C. Psychical dependence.

D. Tolerance.

E. Cumulation of promedol.

6. A patient in the unconscious state was admitted to the emergency room. Skin is cold, pupils are dilated, breathing is heavy, with cycles of the Cheyne – Stokes type, blood pressure is decreased, urinary bladder is overloaded. Poisoning with what substance is the most likely?

A. Narcotic analgesics.

B. M-cholinergic agonists.

C. Nonnarcotic analgetics.

D. Sedatives.

E. M-cholinergic antagonists.

7. A 70-year-old man, who suffered from chronic bronchitis, was prescribed the antitussive drug codeine. What is the mechanism of antitussive effect of this drug?

A. Competitive action.

B. Central effect.

C. Reflex.

D. Local effect.

E. Peripheral effect.

8. A patient was prescribed narcotic analgesic, which is a derivative of cyclohexanol, agonist-antagonist of opiate receptors, a little weaker than morphine. It does not influence the digestive tract, has some analgesic action, and is characteristic of nonnarcotic analgetics; it is not recommended for children under 14. What is this drug?

A. Omnopon.

B. Promedol.

C. Morphine hydrochloride.

D. Tramadol.

E. Codeine phosphate.

9. In 2–3 hours after the parenteral introduction of a drug a patient became comatose. Cheyne – Stokes respiration was observed, pupils became abruptly miotic, knee reflex was kept. What drug could lead to the poisoning?

A. Phenobarbital.

B. Morphine.

C. Diazepam.

D. Aminazine.

E. Ethyl alcohol.

10. An unconscious patient has been taken to a hospital. His skin is cold, pupils are miotic, breathing is complicated (Cheyne – Stokes type), arterial pressure is low, the urinary bladder is overfilled. The diagnosis is poisoning with morphine. What drug is it necessary to give as an antidote?

A. Sodium thiosulfate.

B. Bemegride.
C. Cytitonum.
D. Naloxone.
E. Unithiol.

11. A 35-year-old parturient woman has a pain syndrome connected with the delay of the first labor stage. What drug is necessary to be used for relieving the pain?

A. Promedol.
B. Paracetamol.
C. Analginum (metamizole).
D. Morphine.
E. Codeine.

12. An emergency team has taken a patient demonstrating drowsiness, cyanosis, and infrequent cogged-wheel breathing, sharply miotic pupils to a reception ward. Knee reflexes are kept. The traces of injections are revealed on his arms. What drug causes poisoning characterized by the above-mentioned symptom?

A. Aminazine.
B. Morphine.
C. Atropine.
D. Proserinum.
E. Phenobarbital.

13. A 30-year-old patient after a traffic accident was delivered with a hip bones fracture to a hospital. The patient has low arterial pressure, weak pulse, and increased pain reaction to the least touch in the place of damage. What is necessary to use to prevent the traumatic shock of this patient?

A. Papaverine.
B. Paracetamol.
C. Pentazocine.
D. Analginum (metamizole).
E. Morphine.

14. A 25-year-old woman is hospitalized with signs of acute poisoning with morphine. What antidote is necessary to be given to the patient?

A. Aethymizole.

B. Unithiol.

C. Atropine.

D. Lobeline.

E. Naloxone.

15. A patient with morphine poisoning has been delivered to a hospital. It is known that in case of acute poisoning with morphine a specific antagonist naloxone is used. What factor provides the development of antagonistic action?

A. Decrease of sensitivity of the organism to morphine.

B. Direct excitation of respiratory centre.

C. Reflex excitation of respiratory centre.

D. Sharp acceleration of morphine metabolism.

E. Competition for binding with opiate receptors.

16. Morphine hydrochloride solution has been introduced subcutaneously to a patient with traumatic shock to provide analgesia. What is the mechanism of analgesic effect of this drug?

A. Inhibition of formation of pain mediators in peripheral tissues.

B. Interaction with opiate receptors.

C. Blockade of peripheral sensitive receptors.

D. Change of pain emotional coloring.

E. Abnormality of afferent nerves impulses conduction.

17. A patient suffering from urolithiasis is hospitalized because of an attack of renal colic. What emergency drug is to be prescribed in this case?

A. Contrycal.

B. Promedol.

C. Analginum.

D. Paracetamol.

E. Furosemide.

18. For anaesthesia of labor a doctor prescribed an analgesic. What analgesic is the most expedient to use in this case?

A. Paracetamol.
B. Analginum.
C. Morphine.
D. Fentanyl.
E. Promedol.

19. A specific antagonist of morphine hydrochloride was prescribed to a 15-year-old boy with manifestations of acute poisoning with narcotic analgesics. What is this drug?

A. Bemegride.
B. Naloxone.
C. Tetacinum-calcium (edetate calcium disodium).
D. Pentazocine.
E. Unithiol.

20. Prescribe to patient a drug – a synthetic substitute of morphine, which has a sedative effect, does not spasm muscles and sphincters of the digestive tract, slightly influences the centre of respiration, and reduces the tone of uterus neck.

A. Promedol.
B. Analginum.
C. Omnopon.
D. Fentanyl.
E. Paracetamol.

21. An unconscious patient is hospitalized to a resuscitation unit with symptoms of acute morphine poisoning: hypothermia, Cheyne – Stokes respiration, hypotension, bradycardia, acute miosis. Which of the listed drugs will be the most effective in this case?

A. Caffeine sodium benzoate.
B. Cordiaminum.
C. Camphor.
D. Aethymizole.
E. Naloxone.

22. A 26-year-old patient in coma is brought in intensive care unit. The temperature is 35 °C. The skin is cold. Mucous membranes are cyanotic. Sharply miotic pupils are observed. Respiration is oppressed, as of Cheyne – Stokes type. What drug is the cause of poisoning?

A. Anaprilinum.
B. Proserinum.
C. Adrenaline.
D. Morphine.
E. Atropine.

23. A 60-year-old patient suffers from incurable cancer of the lung with multiple metastases. Choose the drug for pain relief in this patient.

A. Paracetamol.
B. Diclofenac sodium.
C. Analginum.
D. Morphine.
E. Fentanyl.

24. A 20-year-old patient is delivered to an urgent unit with opium poisoning. What the most effective drug should be administered to him?

A. Potassium permanganate.
B. Naloxone.
C. Atropine.
D. Aethymizole.
E. Active carbon.

25. A victim with hip and ribs fractures is delivered to an emergency room after the road accident. What drug should be administered to the patient for prevention of pain shock?

A. Tramadol.
B. Analginum.
C. Nitric oxide.
D. Morphine.
E. Diazepam.

26. A patient with myocardial infarction is delivered to a resuscitation unit. What drug should be administered to the patient for prevention of pain shock?

A. Naloxone.
B. Morphine.
C. Analginum.

D. Paracetamol.

E. Celecoxib.

27. A parturient woman is delivered to an obstetrics department. The doctor administered an opioid analgesic for pain relief to the woman. Indicate this drug.

A. Diclofenac sodium.

B. Acetylsalicylic acid.

C. Promedol.

D. Analginum.

E. Celecoxib.

28. A patient with a serious trauma is delivered to an emergency room. For prevention of pain shock, a doctor administered an opioid analgesic to him. Indicate this drug.

A. Celecoxib.

B. Morphine.

C. Paracetamol.

D. Piroxicam.

E. Acetylsalicylic acid.

29. Antagonist of opioid analgesics was administered to a patient with significant signs of opioid intoxication. Indicate this drug.

A. Fentanyl.

B. Morphine.

C. Promedol.

D. Omnopon.

E. Naloxone.

30. A patient with morphinism is delivered to a narcological unit. In the result of examination, a doctor indicated the decreasing of morphine action. Indicate the name of phenomenon of the drug action weakening in the result of repeated drug administration.

A. Summation.

B. Material cumulation.

C. Tolerance (accustoming).

D. Functional cumulation.

E. Antagonism.

Non-Opioid Analgesics

Non-opioid analgesics are drugs which provide analgesic, anti-inflammatory, and antipyretic effects. Unlike opioid analgesics, these drugs don't cause euphoria and drug dependence.

Non-opioid analgesics are classified as follows:

1. Salicylic acid derivatives (salicylates): *acetylsalicylic acid (aspirin)* and *sodium salicylate.*
2. Pyrazolone derivatives: *analginum (metamizole), butadionum (phenylbutazone),* and *rheumox (azapropazone).*
3. Para-aminophenol derivatives: *paracetamol (acetaminophen).*
4. Indolacetic acid derivatives: *indomethacin* and *sulindac.*
5. Phenylacetic acid derivatives: *ortophenum (diclofenac).*
6. Phenylpropionic acid derivatives: *ibuprofen, flurbiprofen,* and *ketoprofen.*
7. Naphthylpropionic acid derivatives: *naproxen.*
8. Oxicams: *piroxicam, lornoxicam,* and *meloxicam.*
9. Anthranilic acid derivatives: *mefenamic acid, flufenamic acid,* and *meclofenamic acid.*
10. Heteroarylacetic acid derivatives: *ketorolac.*
11. Sulfonanilides: *nimesulide.*
12. Isonicotinic acid derivatives: *amizon (enisamium iodide).*
13. Coxibes: *celecoxib, rofecoxib,* etc.

The mechanism of action of non-opioid analgesics is associated with their ability to block synthesis of prostaglandins by inhibition of enzyme cyclooxygenase. It results in development of anti-inflammatory, antipyretic, and analgesic effects.

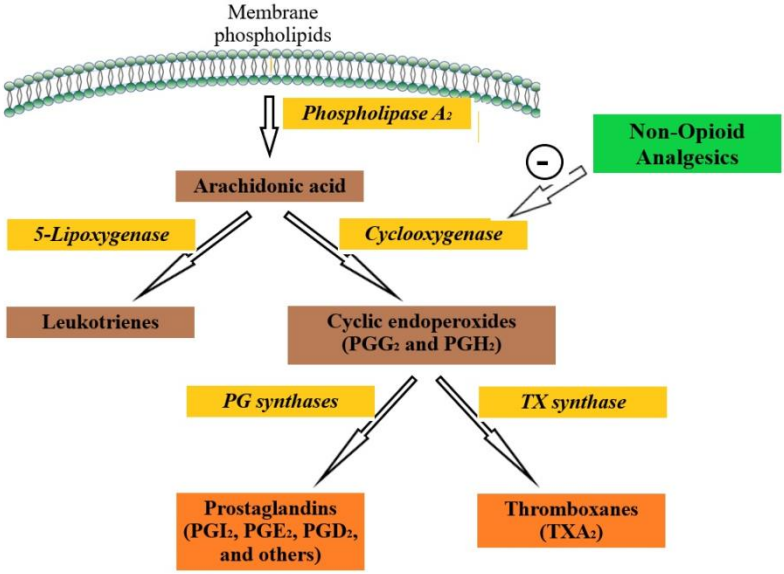

Figure 10 – Mechanism of action of non-opioid analgesics:
PG synthases – prostaglandin synthases;
TX synthase – thromboxane synthase

Analgesic effect of non-opioid analgesics is due to cyclooxygenase inhibition that decreases synthesis of prostaglandins. It is known, that prostaglandins increase sensitivity of nociceptors to chemical and mechanical irritants. The decrease of exudation and oedema in inflammatory region lowers mechanical squeezing of nerve fibers and leads to pain relief. It should be noticed that central component is also a part of analgesic effect of non-opioid analgesics. Analgesia develops in several hours after the drug administration. Analgesic activity of non-opioid analgesics is 15–100 times less than those of opioids. Non-opioid analgesics are effective mainly at pain induced by inflammation. According to the degree of analgesic effect, non-opioid analgesics can be arranged as follows: diclofenac > indomethacin > analginum (metamizole) > ibuprofen > paracetamol > acetylsalicylic acid.

Antipyretic effect of non-opioid analgesics is due to inhibition of cyclooxygenase in the central nervous system that decreases PGE_1

synthesis in hypothalamus. PGE_1 is a potent pyrogen which affects the centre of thermoregulation. At fever, non-opioid analgesics decrease body temperature by the increase of heat emission in result of the dilation of skin blood vessels and increase of perspiration. Antipyretic effect develops in several hours after the drug administration. Most marked antipyretic effect is typical for derivatives of indolacetic acid and for pyrazolone derivatives. It should be noticed that subfebrile temperature is a protective reaction of an organism. Subfebrile temperature does not need an intake of non-opioid analgesics.

Anti-inflammatory effect of non-opioid analgesics also is the result of cyclooxygenase inhibition that decreases synthesis of prostaglandins, prostacyclins, and thromboxanes. Most drugs inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 (constitutive) is constantly present in human cells. This enzyme participates in regulation of normal functional activity of body tissues (synthesis of thromboxane A_2 by thrombocytes, prostacyclin by endothelial cells, prostaglandins by gastrointestinal tract and kidneys, etc.). At normal physiological state, only insignificant amount of COX-2 (inducible) is present in body tissues. But its concentration sharply elevates due to inflammation. COX-2 participates in synthesis of eicosanoids potentiating the activity of mediators of inflammation, as histamine, serotonin, and bradykinin. These bioactive substances irritate pain receptors in an inflammation area, affect the activity of thermoregulation centre, stimulate cellular proliferation and mutagenesis, promote destructive processes. High activity of COX-2 is observed in epithelial cancer cells and in atherosclerotic plaques.

Non-selective inhibitors of cyclooxigenases inhibit the enzyme isoforms to varying degrees. Thus, acetylsalicylic acid and indomethacin have a greater effect on COX-1 than on COX-2, while mephenamic acid and piroxicam inhibit COX-1 to a lesser extent. Diclofenac sodium and naproxen provide the same inhibition of both COX-1 and COX-2. It should be noted that the stronger the COX-1 inhibition, the more often side effects develop.

Recently, selective inhibitors of COX-2 have been created: meloxicam, nabumetone, nimesulide, celecoxib, etc. These drugs are called nonsteroidal anti-inflammatory drugs of II generation.

Inhibition of COX leads to increased utilization of arachidonic acid through lipoxygenase pathway and increased synthesis of leukotrienes which promote vasoconstriction and reduce exudation.

Also, nonsteroidal anti-inflammatory drugs inhibit free-radical reactions and activity of oxygen radicals which promote inflammation due to alteration of cellular membranes in the inflammation area. Besides, these drugs reduce formation of ATP and other macroergic compounds. It is significant, that nonsteroidal anti-inflammatory drugs exhibit cytostatic action that inhibit proliferation in an inflammation area and decelerate sclerotic process.

Non-opioid analgesics restrict exudation and proliferation. These agents have little influence upon the stage of alteration. Anti-inflammatory effect develops in several days after the start of a drug intake. The derivatives of pyrazolone (except analginum) have the most marked anti-inflammatory effect. Significant anti-inflammatory action also is typical for high doses of salicylates, for derivatives of phenylacetic acid, and for phenylpropionic acid.

Desensitizing effect develops in several months of a constant intake of nonsteroidal anti-inflammatory drugs. This effect is not used in medicine.

Anti-aggregative effect develops in the result of a decrease of thromboxane A_2 synthesis. This effect is most prominent in acetylsalicylic acid. Therefore, this drug is used to prevent platelet aggregation and thrombosis.

Anticancerogenic effect is typical only for selective COX-2 inhibitors (celecoxib, rofecoxib). This effect is shown concerning epithelial malignant tumors.

Selective COX-2 inhibitors also slow down the progress of atherosclerosis (*anti-aterogenic effect*).

Non-opioid analgetics inhibit contractile activity of both pregnant and nonpregnant uterus.

The main route of administration of non-opioid analgesics is oral one. Drugs should be given after meals. Some agents are also administered parenterally: acelysin (salicylic acid derivative) – intramuscularly or intravenously; meloxicam – intravenously; diclofenac sodium – intramuscularly.

Non-opioid analgesics are readily absorbed in gastrointestinal tract. The maximal concentration in blood is accumulated in 0.5–2 hours after a drug intake. The degree of the drug binding with plasma proteins is up to 80–99 %. Average duration of action is 6–8 hours. As a rule, non-opioid analgesics are prescribed 3–4 times a day. The drugs with prolonged action (oxicams, sulindac) are prescribed once a day. Non-opioid analgesics undergo the biotransformation in the liver. The degree of biotransformation is 90–97 %.

There is a danger of accumulation of toxic metabolites of non-opioid analgesics in the body. Thus, at viral infections (especially in children and teenagers), accumulation of toxic metabolites of acetylsalicylic acid can induce the development of Reye's syndrome. It is a potentially fatal syndrome that characterized by toxic encephalopathy, acute fat dystrophy of the liver, brain, and kidneys. Therefore, acetylsalicylic acid is contraindicated to children and teenagers with either chickenpox or influenza. Accumulation of paracetamol metabolites leads to hepato- and nephrotoxicity that develops in 1–2 days.

Indications for the use of non-opioid analgesics are as follows:

1) pain at small and moderate traumas of soft tissues, dislocations, sprain or rupture of ligaments, bone and joint bruises, etc.;

2) postoperative pain (as a rule, drugs are administered parenterally);

3) headache;

4) toothache;

5) myositis, neuralgia, arthralgia, and radiculitis;

6) pain at a spasm of urinary or biliary tracts (colics), and pancreatitis;

7) rheumatic diseases;

8) gout;

9) fever.

The following side effects are observed at the therapy with non-opioid analgesics:

1. Nausea, vomiting, epigastral pain, ulcers of stomach, and intestinal erosies. These complications are associated with inhibition of prostaglandin synthesis in gastric and intestinal mucous membranes. It is known that prostaglandins exhibit protective action upon mucous mebranes of gastrointestinal tract: reduce secretion of hydrochloric acid, increase secretion of mucous and bicarbonate, improve microcirculation, promote tissue regeneration.

2. Aspirin-induced asthma or Fernand-Widal triad is a result of predominant transformation of arachidonic acid by lipoxygenase pathway and synthesis of leukotrienes. This syndrome is manifested by nasal polyposis, rhinitis, asthma attacks, and urticaria.

3. Edemas are associated with fluid and electrolytes retardation due to inhibition of cyclooxygenase in renal tubules. This complication developes in 4–5 days after the start of a drug intake. Among non-opioid analgesics, butadionum and indomethacin most commonly cause this complication.

4. Blood dyscrasias are manifested by leucopenia, agranulocytosis, thrombocytopenia, and seldom – erhythrocytopenia. Most commonly these complications arise due to intake of pyrasolone derivatives (e. g., analginum).

5. Paracetamol can provoke methemoglobinemia in children under 1-year-old or in persons with genetic predisposition.

6. Hemoragic syndrome develops owing to intake of acetylsalicylic acid, because this drug exhibits anti-aggregative and anticoagulative properties (due to antagonism with vitamin K, aspirin violates synthesis of II, VII, IX, and X clotting factors in the liver).

7. Retinopathy and keratopathy may develop as a result of indomethacin deposition in retina and cornea of eyes.

Salicylic Acid Derivatives (Salicylates)

Salicylic acid derivatives are *acetylsalicylic acid, methyl salicylate,* and *sodium salicylate.* Acetylsalicylic acid (aspirin) is

used most commonly among them. Salicylates exert anti-inflammatory, analgesic, and antipyretic effects.

Salicylic acid exhibits a marked local irritative activity and is used in dermatology. High concentrated salicylic acid (10–20 %) causes rejection of epidermis and is used for elimination of callus. 1–2 % salicylic acid promotes epidermis regeneration (keratoplastic action). Salicylic acid inhibits secretion of sweat glands and is used at increased sweating. Also, salicylic acid has antibacterial action and is used as antiseptic agent.

Methyl salicylate is used as a component of ointments for treatment of arthritis, myositis, and exudative pleuritis.

Sodium salicylate is used as antirheumatic agent. The drug exhibits mild analgesic and antipyretic effects.

Acetylsalicylic acid (*aspirin*) has higher analgesic and antipyretic effects than sodium salicylate. Taken orally aspirin begins to be absorbed in the stomach. Speed of absorption depends on pH. Thus, change of gastric pH to alkaline side leads to deceleration of aspirin absorption. Maximal blood concentration of aspirin is observed in 2 hours after the drug intake. Aspirin easely penetrates through tissue barriers. About 50–80 % of an absorbed aspirin binds with plasma proteins. Aspirin undergoes hepatic metabolism by conjugation with glucuronic acid or glycin. Metabolites are excreted with urine.

Anti-inflammatory and antirheumatic effects of acetylsalicylic acid is associated not only with violation of prostaglandin synthesis. High doses of aspirin stimulate secretion of corticotropin and glucocorticoids, that also promotes anti-inflammatory effect. Activity of hyaluronidase is inhibited resulting in the decrease of vascular permeability, slow-down of leukocyte migration, and reduction of oedema. Also, aspirin inhibits proliferation owing to violation of conjugation of tissue respiration and phosphorylation.

High doses of salicylates stimulate respiration due to direct excitation of the respiratory centre and increase of carbonic acid synthesis in tissues. The increase of frequency and amplitude of breathing may result in respiratory alkalosis.

Salicylates stimulate bile secretion in a liver. High doses of salicylates increase uric acid excretion due to reduction of its reabsorption. This effect is used in the treatment for gout. It should be noticed that low doses of acetylsalicylic acid suppresse only secretion of uric acid that results in the increase of uric acid concentration in the blood.

Aspirin decreases manifestations of allergic reactions owing to inhibition of histamine release and reduction of antibody synthesis, including autoantibodies. Also, its anti-inflammatory effect is an important at treatment of inflammation of allergic origin, including nephritis, rheumatism, and other collagenoses.

Antiaggregatory effect of acetylsalicylic acid is due to inhibition of cyclooxygenase and decrease of thromboxane A_2 synthesis. Aspirin also decreases the level of prothrombin in blood owing to disorder of vitamin K metabolism. Acetylsalicylic acid is widely used to prevent platelets aggregation and thrombosis at ischemic heart disease, myocardial infarction, and ischemic stroke.

Acetylsalicylic acid slows down the synthesis of lipids and accelerates the catabolism of lipids and carbohydrates. In diabetic patients, aspirin decreases the level of glucose in blood.

Acetylsalicylic acid is used at moderate pain and inflammatory processes: myalgia, headache, toothache, dysmenorrhea, gout, fever, etc.

The most serious side effect of acetylsalicylic acid is ulcerogenic action (ability to cause the development of stomach ulcers and gastritis). Ulcerogenic action is due to COX-1 inhibition, that leads to the decrease of prostaglandin synthesis by mucous membrane of stomach. It is known, that prostaglandins inhibit hydrochloric acid secretion, stimulate synthesis of mucous, and improve microcirculation in mucous membrane of stomach.

Besides, the allergic reactions (even anaphylactic shock) and aspirin-induced asthma are also possible. The intake of aspirin by a pregnant woman can cause vascular disorders in lungs of the fetus. Mutagenic effect of acetylsalicylic acid is also possible.

Long-time therapy with aspirin can cause chronic intoxication by aspirin – salicylism. Symptoms of salicylism include such disorders as ringing in the ears (tinnitus), hearing impairment, vertigo, headache, and bronchospasm (especially in asthmatics).

At acute poisoning by aspirin the following symptoms are observed: tinnitus, nausea, vomiting, stomach pain, impairment of hearing and vision, general weakness, anxiety, incoherent speech, etc. Sometimes, hallucinations and convulsions are also possible. Salicylate-induced stimulation of respiration leads to hyperventilation. Breathing becomes deep and frequent (Kussmaul breathing), that can cause respiratory alkalosis. Respiratory alkalosis is replaced by metabolic acidosis due to inhibition of tricarboxylic acid cycle, accumulatin of organic acids and ketone bodies. Toxic doses of aspirin accelerate glycogenolysis and inhibit glycogenesis that leads to hyperglycemia and glycosuria. Hypokalemia and hyponatremia develop in tissues, body temperature is elevated.

Treatment includes alkalinization of the urine, forced diuresis, fluid replacement, gastric lavage with activated charcoal, hemodialysis, and artificial ventilation. It should be noticed that furosemide, as a rule, does not promote salicylates excretion, because its diuretic effect is associated with increased synthesis of prostaglandins in kidneys. But this synthesis is blocked by salicylates. For stimulation of hepatic biotransformation of salicylates, 20 % glucose solution is administered intravenously. Diazepam is used to stop convulsions. At hypoxia, oxigenotherapy is provided.

Pyrazolone Derivatives

Pyrazolone derivatives are *phenylbutazone (butadionum), metamizole (analginum),* and *azapropazone (rheumox).* Drugs have anti-inflammatory, analgesic, and antipyretic effects. Pyrazolone derivatives have mechanism of action similar to salicylates. Most expressed blockage of cyclooxygenase is observed in the central nervous system; therefore, central mechanism of action plays an important role in analgesic effect of pyrazolone derivatives. Besides, these drugs are effective at gout and inhibit hemocoagulation.

Because pyrazolone derivatives can cause agranulocytosis, long-time therapy with these drugs needs control of blood. Nowadays, pharmaceutical production of pyrazolone derivatives is significantly restricted.

Butadione has a high anti-inflammatory effect. The drug is administered perorally and is used locally in ointments. In case of oral intake, butadione is easily absorbed from gastrointestinal tract. Biotransformation of butadione occurs in liver. Metabolites are excreted by kidneys. Butadione is accumulated in the body, because its period of the half-life is about 1 day.

Butadione is used to treat arthritis, gout, tendovaginitis, rheumatoid arthritis, radiculitis, thrombophlebitis, etc. Butadione is highly toxic agent. The most common and serious side effect is ulceration of gastrointestinal tract. Also, the drug inhibits diuresis and causes edemas. Long-time drug intake (during several months) can cause aplastic anemia, leukopenia, and agranulocytosis. Sometimes, allergic reactions, neuritis, and myocardiodystrophy are possible.

Anti-inflammatory effect of *analginum* is less, than those of butadionum. But analginum exhibits marked analgesic and antipyretic effects. The drug is administered both perorally and parenterally (intramuscularly and intravenously). Indications for use are moderate pain at inflammations, postoperative pain, and fever.

Para-Aminophenol Derivatives

Para-aminophenol derivative *paracetamol* exhibits analgesic and antipyretic effects but lacks anti-inflammatory effect. Paracetamol is commonly combined with codeine and salicylates to treat headache, migraine, myalgia, neuralgia, and fever. Paracetamol violates synthesis of prostaglandins only in the central nervous system. The drug does not influence prostaglandin synthesis in peripheral tissues.

Paracetamol is primarily metabolized by conjugation in the liver and is quickly excreted through kidneys.

Therapeutic doses of paracetamol seldom cause side effects. But the drug has narrow therapeutic index. In case of paracetamol overdose, metabolism by conjugation becomes saturated, and

paracetamol is oxidated by the cytochrome P_{450} to N-acetyl-p-benzoquinone imine. This metabolite conjugates with glutathione and is excreted through kidneys. But in situation of gluthatione deficiency, N-acetyl-p-benzoquinone imine interacts with cysteinyl sulfhydryl groups of cellular proteins. This interaction leads to mitochondrial dysfunction, liver inflammation and necrosis. Similar pathological processes occur in kidneys and myocardium. The first symptoms of paracetamol overdose (nausea and vomiting) occur in 12–24 hours.

In adults, acute poisoning can result from oral ingestion of paracetamol at a dose of 150–200 mg/kg (about 7.5-10 g) over 24 hours.

Acetylcysteine is used to treat poisoning by paracetamol. The drug should be administered during first 12 hours after poisoning that allows to avoid formation of toxic metabolites in the liver.

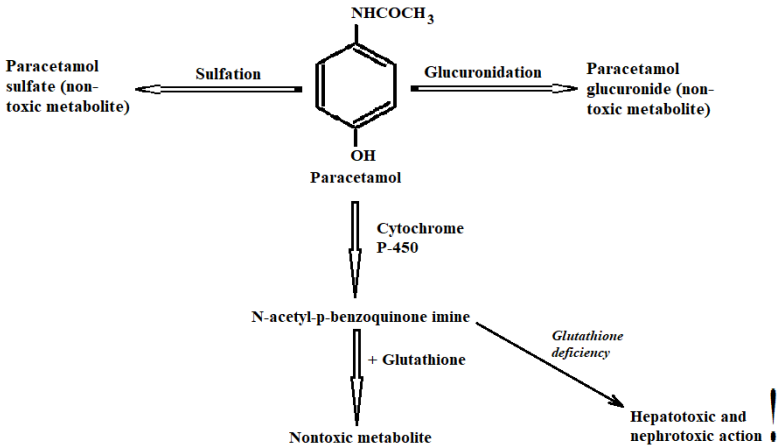

Figure 11 – Paracetamol biotransformation pathways

Paracetamol is widely used in pediatric practice to treat children under 12-years-old, because in this age cytochrome P_{450} system is insufficiently developed and the drug biotransformation occurred owing to conjugation with sulphates without formation of toxic metabolites. It should be noticed that maximal daily therapeutic dose of paracetamol is 4 g for adults and 0.09 mg/kg for children.

Indolacetic Acid Derivatives

Indomethacin and *sulindac* are derivatives of indolacetic acid.

Indomethacin is widely used in medicine. The drug exhibits marked anti-inflammatory and antipyretic effects. Analgesic effect is less expressed. Indomethacin is taken orally or administered rectally. The drug is readily absorbed from gastrointestinal tract. Its maximal concentration in the blood is observed in 2 hours after intake. Indomethacin binds with plasma proteins in high degree and slowly penetrates the tissues. But the drug easily penetrates through placenta. Indomethacin is metabolized in the liver. About 5–10 % of unchanged drug is excreted through kidneys. The half-life of indomethacin is about 2 days.

Indomethacin is used to treat gout, collagenoses, rhumatoid arthritis, osteoarthritis, inflammatory diseases of kidneys, glomerulonephritis, rheumatism, etc. Therapeutic effect develops in dependence on severity of disease. At rheumatism, pain is eliminated in several days, but at rheumatoid arthritis effect develops in several weeks. Early cancellation of the drug intake leads to restoration of disease symptoms.

Indomethacin is a highly toxic drug. Its side effects are headache, vertigo, depressions, hallucinations, dyspeptic disorders (gastral pain, nausea, vomiting, diarhea, ulceration of mucosa, and gastritis), vision disorders, allergic reactions, and bronchospasms. Indomethacin slows down the blood coagulation, violates platelet aggregation, and inhibits hemopoiesis. Also, the drug retains water in the body that leads to oedemas. Toxic damage of liver and pancreas is also possible. Indomethacin is contraindicated for children under 7 years.

Phenylacetic Acid Derivatives

Diclofenac sodium (*Voltaren*), and *fenclofenac* are derivatives of phenylacetic acid.

Diclofenac sodium has a high anti-inflammatory activity and long duration of action. Also, diclofenac sodium exhibits marked analgesic and antipyretic effects. The drug is used to treat

inflammations of different localization: rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondyloarthritis, osteoarthritis, gout, etc. This drug is characterized by low toxicity. Side effects are dyspeptic disorders and allergic reactions.

Phenylpropionic Acid Derivatives

This group includes such drugs as *ibuprofen, naproxen,* and *nabumetone.*

Ibuprofen exhibits marked anti-inflammatory, antipyretic, and analgesic effects. Anti-inflammatory effect of ibuprofen is higher than those of salicylates, but less than anti-inflammatory effect of indomethacin. Ibuprofen is taken orally in the treatment for rheumatism, rheumatoid arthritis, osteoarthrosis, ankylosing spondylitis, etc. Its effect is better if the drug is prescribed in an initial stage of the disease. Ibuprofen is a drug with low toxicity. The main side effects of ibuprofen are dyspeptic disorders, mild hepatotoxicity, and neurotoxicity.

Naproxen is most commonly used as antipyretic agent (its efficacy is higher than that of aspirin). Also, naproxen is used to treat inflammatory diseases, but its anti-inflammatory activity is less than the activity of diclofenac sodium.

Anthranilic Acid Derivatives

Mefenamic, flufenamic, and *meclofenamic acids* are representatives of this group. These drugs are characterized by the marked antipyretic effect, which is equal to the aspirin efect. Sodium salt of mefenamic acid exhibits a marked and long-lasting analgesic effect at toothache. These drugs are inductors of interferon and exhibit an antiallergic action. Indications for use of anthranilic acid derivatives are rheumatism, nonspecific polyarthritis, artralgia, myalgia, headache, stomatitis, paradontosis, etc.

Side effects of anthranilic acid derivatives are like those of other non-steroid anti-inflammatory drugs. But these drugs seldom cause

ulceration of gastrointestinal tract. Long-time use of anthranilic acid derivatives leads to albuminuria, leukocyteuria, and erythrocyteuria.

Oxicam Derivatives

This group includes such agents as *piroxicam, lornoxicam,* and *meloxicam.*

Piroxicam is taken orally once a day. The maximum drug concentration in the blood is observed in 3–5 hours after an oral intake. The degree of drug binding with plasma proteins is very high. The drug has long-lasting effect. Its metabolites and insignificant amount of the unchanged drug are excreted through kidneys. The half-life of piroxicam is 75 hours. The drug is used to treat rheumatism, osteoarthritis, ankylosing spondylitis, etc. Sometimes, a course of treatment lasts up to 2 years. Side effects of piroxicam are dispetic disorders and hemorrhages.

Meloxicam is characterized by a significantly higher ability to inhibit COX-2 than COX-1. The drug is taken orally or administered rectally. Its indications for use are arthrites, arthroses, and other inflammatory diseases. Side effects of meloxicam are nausea, vomiting, stomachache, skin rash, headache, dizziness, erosions of gastrointestinal tract, hepatotoxicity, etc.

Sulfonanilides

Nimesulide blocks mainly COX-2. The drug exhibits anti-inflammatory, analgesic, and antipyretic effects. Additionally, nimesulide has antioxidant action. Nimesulide is used to treat posttraumatic pain, rheumatoid arthritis, toothache, myalgia, osteoartoses, etc. Its negative influence upon gastrointestinal tract is low.

Isonicotinic acid derivatives

Amizon shows anti-inflammatory, antipyretic, analgesic, and immunomodulating effects. Anti-inflammatory and antipyretic effects of amizon are identical to those of aspirin. Its analgesic effect, in a significant degree, is associated with inhibition of the pain impulse

transmission through a reticular formation. Immunomodulating effect is manifested by the increase of both humoral and cellular immunity. Titre of antibodies and endogenous interferon in the blood plasma are 3–4 times increased. Also, amizon increases the activity of macrophages and T-lymphocytes. Amizon is an active peroral inductor of endogenous interferon.

Amizon does not exhibit ulcerogenic action and has no toxic influence upon blood and parenchymatous organs.

Amizon is used in the treatment and prevention of the following diseases:

– influenca and other respiratory infections, including children who are long and often sick;

– viral and bacterial pneumonias, infectious mononucleosis, and tonsillitis;

– measles, rubella, chicken pox, scarlet fever, parotitis;

– cutaneous-articular form of erysipeloid (infectious disease caused by *Erysipelotrix rhusiopathiae*) and felinosis or cat-scratch disease (infectious disease caused by *Bartonella henselae*);

– meningitis and meningoencephalitis of viral and bacterial origin, chronic brucellosis, and typhoid fever;

– herpetic and adenoviral infections: keratitis, uveitis, conjunctivitis, and keratoconjunctivitis;

– pain syndrome at osteochondrosis, artralgia, neuralgia, and herniation of the intervertebral disc;

– acute and chronic inflammatory processes in surgical and obstetric-gynecological practice.

The intake of amizon together with high doses of ascorbic acid and other vitamins-antioxidants is the most advisable.

For treatment of influenca and other infectious respiratory diseases, adults take amizon orally in a dose 0.25–0.5 g (1–2 tablets) after meals 2–4 times a day during 5–7 days. A preventive dose is 1 tablet daily during 3–5 days, further – 1 tablet once per 2–3 days during 2–3 weeks.

Amizon is a drug with low toxicity. Its side effects are insignificant oedemas of mucous membranes, allergic reactions, and bitter taste in the mouth.

Amizon is contraindicated at hypersensitivity to iodine. The drug is not prescribed to children under 6 years old and to pregnant women during the first trimester.

Coxibs

Celecoxib, rofecoxib, etoricoxib, valdecoxib and its prodrug *parecoxib* are COX-2 selective inhibitors. Their affinity to COX-2 is hundreds of times more than the affinity to COX-1.

Celecoxib exerts anti-inflammatory, analgesic, and antipyretic effects, but lacks anti-aggregant action. The drug prevents the development of cancer and polyposis of colon and rectum. Celecoxib is taken orally. The drug is readily absorbed from gastrointestinal tract. Biotransformation of celecoxib is occurred in liver. The drug and its metabolites are excreted mainly with bile. Celecoxib is used to treat osteoarthritis, rheumatoid arthritis, and other collagenoses. Also, celecoxib is used in the complex treatment for familial adenomatous polyposis of the large intestine and for prevention of the colorectal cancer.

Side effects of celecoxib are presented mainly by allergic reactions. Gastrointestinal lesions are observed seldom. Sometimes, nephrotoxicity, anemia, and inhibition of hepatic function are occurred.

Currently, there is evidence of cardiotoxicity of rofecoxib and valdecoxib. Prolonged use of these drugs increases the incidence of myocardial infarction. It is possible that this phenomenon is caused by the activation of clot formation due to a decrease in the plasma concentration of prostacyclin. Therefore, drugs of this pharmacological group should be prescribed with caution in patients with an increased risk of thrombosis.

Table 16 – Drugs for prescription

Drug name	Single dose and mode of administration	Drug product
Acidum acetylsalicylicum	Orally 0.25–1 g 3–4 times a day	Tablets 0.1; 0.25 or 0.5 g
Analginum	Orally 0.25–0.5 g 2–3 times a day; intramuscularly or intravenously 0.25–0.5 g 2–3 times a day	Tablets 0.5 g; ampoules 1 ml or 2 ml of 25 or 50 % solution
Butadionum	Orally 0.1–0.15 g 2–4 times a day; for topical application as 5 % ointment	Tablets 0.15 g; 5% ointment
Diclofenac-natrium	Orally 0.025–0.05 g 1–3 times a day; intramuscularly 0.075 g once a day	Coated tablets 0.025 g; ampoules 3 ml of 2.5 % solution
Paracetamolum	Orally 0.2–0.4 g 2–3 times a day	Tablets 0.2 g
Celecoxib	Orally 0.1–0.2 g	Tablets 0.1 g
Ibuprofenum	Orally 0.2–0.4 g	Coated tablets 0.2, 0.4 and 0.6 g

Step 1. Tasks for Self-Control
Non-Opioid Analgesics

1. After the use of acetylsalicylic acid a patient developed epigastric pain because of exacerbation of his ulcer. What is the cause of ulcerogenic action of this medication?

A. Stimulation of pepsin secretion.
B. Spasm of vessels.
C. Immunosuppressive effect.
D. Anti-prostaglandin effect.
E. Cholagogic effect.

2. Aspirin has anti-inflammatory effect due to inhibition of the cyclooxygenase activity. The level of what biological active compounds will decrease?

A. Biogenic amines.

B. Catecholamines.

C. Leukotrienes.

D. Iodothyronines.

E. Prostaglandins.

3. Signs of gastropathy develop in the patient with rheumatoid arthritis who was treated with indomethacin. What activity of the drug causes this complication?

A. Antihistamine.

B. Antiserotonin.

C. Anticyclooxygenase.

D. Local irritating.

E. Antikinine.

4. A child with hyperthermia has been prescribed a drug, which is an active metabolite of phenacetine and has a strong antipyretic action. It can be inactivated by conjugation with glutathione. In toxic doses it can damage liver cells. Antidotes in case of poisoning are acetylcysteine and methionine. What is this drug?

A. Phenobarbital.

B. Atropine sulfate.

C. Paracetamol.

D. Armine.

E. Caffeine sodium benzoate.

5. A patient with a headache was prescribed a drug – a derivative of pyrazolone which has analgesic and antipyretic action. It has negative influence on haemopoiesis in case of long application. It is forbidden as monotherapy in the countries of the Schengen Agreement. What is this drug?

A. Aethymizole.

B. Analginum.

C. Paracetamol.

D. Pyracetam.

E. Aminazine.

6. A patient with arthritis of a knee joint also suffers from the gastric ulcer. What drug is preferable to relieve pain in the knee joint for this patient?

A. Tramal.

B. Analginum.

C. Aspirin.

D. Promedol.

E. Celecoxib.

7. A 25-year-old patient used a non-opioid analgesic from the group of aniline derivatives for the toothache relief. What is this drug?

A. Ibuprofen.

B. Acetylsalicylic acid.

C. Analginum.

D. Butadionum.

E. Paracetamol.

8. The prolonged use of a non-steroid anti-inflammatory drug in a patient with arthritis and varicose phlebectasia has caused the thrombosis of skin veins. Indicate the drug which can cause this complication.

A. Celecoxib.

B. Ibuprofen.

C. Indomethacin.

D. Aspirin.

E. Butadionum.

9. A patient with fever was delivered to an infectious unit. The non-opioid analgesic – a derivative of salicylic acid – is prescribed to the patient. Indicate this drug.

A. Acetylsalicylic acid.

B. Diclofenac sodium.

C. Analginum.

D. Ibuprofen.

E. Paracetamol.

10. A patient with acute respiratory viral disease and hyperthermia is delivered to an infectious unit. What drug should be prescribed for decrease of temperature?

A. Retabolil.

B. Ambroxol.
C. Salbutamol.
D. Adrenaline.
E. Paracetamol.

11. For decreasing gastric mucosa damage possibility, the non-steroid anti-inflammatory agent – selective inhibitor of COX-2 – is prescribed to a patient with rheumatoid arthritis. Indicate this drug.

A. Ibuprofen.
B. Analginum.
C. Acetylsalicylic acid.
D. Celecoxib.
E. Butadionum.

12. Indicate a drug, the therapeutic effects of which are the result of prostaglandins synthesis inhibition.

A. Acetylsalicylic acid.
B. Morphine.
C. Fentanyl.
D. Carbamazepine.
E. Lithium salts.

13. A female consulted in a doctor about pain and limited movements in the knee joints. Which of the following non-steroid anti-inflammatory drugs should be administered taking into consideration that the patient has a history of chronic gastroduodenitis?

A. Acetylsalicylic acid.
B. Promedol.
C. Butadionum.
D. Diclofenac sodium.
E. Celecoxib.

Anticonvulsants

Anticonvulsants are drugs which inhibit the function of motor centres and are used in the treatment for convulsions of different origin.

Anticonvulsants are divided into the following groups:

– drugs for symptomathic treatment of convulsions;

– antiepileptic drugs;

– antiparkinsonic drugs.

Drugs for Symptomatic Treatment of Convulsions

There are different causes of convulsions: intoxication by medicines (strychnine, corazole, bemegride, novocaine, etc.) or poisons (insecticides, phosphorus-organic compounds, etc.), infectious diseases (meningitis, influenca, etc.), and others. Convulsions can have clonic or tonic character.

The following groups of drugs are most commonly used in the treatment for convulsive attacks: general anaesthetics, hypnotic drugs, tranquilizers, peripheral myorelaxants, and magnesium sulfate.

Diazepam (sibazon, relanium, seduxen) is most commonly used to eliminate convulsions of different origins. For this purpose, 2 ml of 0.5 % diazepam solution is administered intramuscularly. Diazepam activates GABA-ergic synapses in the central nervous system. The drug inhibits convulsive activity in hippocampus, reduces activation of pyramidal cells of cortex and neurons of cerebellum. High doses of diazepam exhibit myorelaxating action due to inhibition of motoneurons of the spinal cord.

Derivatives of barbituric acid – *thiopental sodium* and *hexenal* – are also commonly used to cessate convulsions. These drugs are administered intravenously, sometimes – intramuscularly or rectally. The main mechanism of their action is associated with inhibition of motor cortex, hippocampus, afferent pathways, and polysynaptic reflexes of the spinal cord. A significant restriction for the use of barbiturates is their depressive influence upon the respiratory centre and inhibition of vasomotor centre.

Sometimes, *chloral hydrate* is administered rectally as anticonvulsant. But its effect develops in 40–60 minutes, therefore, chloral hydrate is more commonly used to prevent recurrent seizures.

Magnesium sulfate is also used to interrupt convulsions. The drug is administered intravenously or intramuscularly. Magnesium ions replace calcium ions in the synapses. It leads to dissociation between the excitation of presynaptic membrane and mediator release into synaptic cleft in the central nervous system, including motor centres of cortex. Impulses transmission in polysynaptic neuronal chains, including convulsive foci, is violated. It should be noticed that intravenous administration of magnesium sulfate should be slow due to the risk of respiratory depression.

If administration of the drugs mentioned above does not lead to cessation of convulsions, inhalation anaesthetic *nitrous oxide* may be used. In severe cases, peripheral myorelaxants (*tubocurarine*, etc.) together with general anaesthetics are administered; but patients receiving such therapy need artificial ventilation.

Antiepileptic Drugs

Epilepsy is a common neurological disease affecting about 1 % of human population. There are several forms of epilepsy; the main among them are grand mal epilepsy (tonic-clonic seizures), petit mal epilepsy (or absence seizures), and psychomotor epilepsy (partial seizures).

Grand mal epilepsy occurs in the form of tonic-clonic convulsions with loss of consciousness and bite of the tongue. Patient falls down and can be injured. Convulsions last several minutes. When convulsions occur, breathing stops. After convulsions, relaxation of skeletal muscles occurs, falling back of the tongue is possible. Convulsions can occur again in a short-time interval. In the future, this episode is expunged from memory. As a rule, sleepiness develops after attack of convulsions.

Petit mal epilepsy is characterized by a short-time (3–15 secunds) loss of consciousness, atony or twitching of some skeletal

muscles without convulsions. A patient can fall and be injured. Eventually, rapidly progressing psychical disorders develop in such patients.

Psychomotor epilepsy attacks occur against the background of clear consciousness. This form of epilepsy is not accompanied by convulsions or myoclonus. Vegetative, visual, auditory, or motor disorders suddenly develop in a patient. Sometimes, attacks are accompanied by psychical disorders, memory impairment, thought disorder, and abnormal behaviour. Outwardly, it looks like meaningful and ordered actions (transportation trip, etc.). In the future, this episode is completely expunged from memory.

Epilepsy is due to the damage of brain tissue (neurons and cells of neuroglia) in result of a cranial trauma, infectious or inflammatory diseases, disorders of cerebral circulation, intoxication, etc. Also, hereditary predisposition is essential. In the lesion area, a part of neurons dies. But, some viable and pathologically changed neurons are between the dead cells and in peripheria of a lesion. These pathologically changed neurons form epileptic focus. The damage of neuronal membranes leads to disfunction of Na^+, K^+-ATPase with the following deceleration of sodium and calcium outflow from the cells. The release of excitatory neurotransmitters increases.

According to the chemical structure, antiepileptic drugs are classified as follows:

1) barbituric acid derivatives: *phenobarbital, primidone (hexamidine),* and *enzobarbital (benzonal)*;

2) hydantoins: *diphenine (phenytoin)*;

3) suxinimides: *ethosuximide*;

4) benzodiazepines: *clonazepam, diazepam,* and *nitrazepam*;

5) valproic acid derivatives: *sodium valproate*;

6) iminostilbene derivatives: *carbamazepine*;

7) GABA derivatives: *vigabatrine*;

8) antagonists of excitatory amino acids: *lamotrigine.*

There is a classification of antiepileptic drugs according to their clinical use:

1) drugs which are used to treat grand mal epilepsy: *phenobarbital, diphenine (phenytoin), hexamidine (primidone), carbamazepine, sodium valproate (valproic acid), lamotrigine,* and *topiramate.*

2) drugs which are used in the treatment for petit mal epilepsy: *ethosuximide, sodium valproate, clonazepam, lamotrigine,* and *trimethadione (trimethine).*

3) drugs which are used to treat psychomotor (partial) epilepsy: *carbamazepine, diphenine (phenytoin), phenobarbital, sodium valproate (valproic acid), hexamidine (primidone), clonazepam, lamotrigine, topiramate, vigabatrine, gabapentin, tiagabine,* and *chloracon (beclamide).*

Antiepileptic drugs exhibit different mechanisms of action which are characterized by the following components:

1. Restoration of properties of neuronal membranes in the epileptic focus by means of keeping resting potential, blockage of sodium channels, inhibition of pathological automatism of neurons in epileptic focus. Inhibition of activity of mitochondrial NADH-dehydrogenase and reduction of cellular energy exchange are also quite important. This mechanism is typical for *diphenine, carbamazepine, sodium valproate,* and *topiramate.*

2. Blockage of T-type calcium channels that leads to reduction of neuronal exitability in epileptic focus owing to: *ethosuximide, trimethadione, sodium valproate.*

3. Increase of inhibitory control under excitatory impulses in epileptic focus by means of GABA-ergic inhibitory mechanism. There are 4 groups of drugs which influence GABA-ergic system:

– drugs improving affinity of GABA to $GABA_A$-receptors (*benzodiazepines, phenobarbital,* and *topiramate*);

– drugs which promote GABA synthesis and prevent its inactivation (*sodium valproate*);

– drugs violating GABA inactivation (*vigabatrine*);

– drugs promoting accumulation of GABA by means of inhibition of its neuronal uptake (*tiagabine*).

4. Influence upon synthesis and release of excitatory amino acids and receptor sensitivity to them. This mechanism is typical for *lamotrigine* and *topiramate*. Lamotrigine breaks down the release of excitatory amino acids (e. g., glutamate) from presynaptic nervous endings. Topiramate blocks glutamatergic receptors.

There are the following main principles of the epilepsy treatment:

1. Treatment should be started as soon as possible, but not later than 1 year after appearance of first symptoms of the disease.

2. Patient treatment starts as monotherapy. It allows to consider drug pharmacokinetics better and to diagnose side effects and complication early.

3. Initial dose prescribed to a patient is 1/3 of full reccomemded therapeutic dose. Further, this initial dose is increased by 1/3 every 5–7 days up to the full therapeutic dose. If the patient does not tolerate the medication, the daily dose is divided into 4–6 intakes. If side effects continue to increase, the taken drug is replaced by another one. In this case, the dose of the first drug is gradually reduced during 3–7 days with simultaneous elevation of a dose of another drug. Any violation of the therapeutic scheme can provoke epilepsy attack. Sudden discontinuation of a drug intake is unacceptable, because it can result in epileptic status and patient's death.

4. At disappierence of clinical symptoms of epilepsy, continuous treatment lasts 3–4 years. After this, doses of drugs are gradually decreased up to full discontinuation of intakes. It should be noticed that full cure as a rule is impossible. In general, children demonstrate better treatment response.

Phenobarbital is one of the main antiepileptic drugs for treatment of grand mal epilepsy. It is a derivative of barbituric acid. The drug also exhibits sedative and hypnotic effects. Its mechanism of action is associated with interaction with barbiturate part of benzodiazepine-barbiturate-$GABA_A$ receptor complex that leads to the increase of GABA affinity to $GABA_A$-receptor. Due to this

mechanism, phenobarbital inhibits both epileptic focus and propagation of pathological impulses from it. At epilepsy, phenobarbital is used in subhypnotic doses. The drug is accumulated in the body. Long-time intake of phenobarbital can lead to the tolerance and drug dependence.

Diphenine is also used to treat grand mal epilepsy. The drug blocks sodium entrance in neurons that suppresses generation of pathological impulses in epileptic focus and their propagation. Taken orally diphenine is readily absorbed from gastrointestinal tract. Biotransformation of the drug is occurred in the liver. Diphenine is an inductor of microsomal enzymes. The drug is accumulated in the body. Side effects of diphenine are dizziness, hyperthermia, nausea, vomiting, tremor, nystagmus, allergic reactions, gingival hyperplasia (occurs in up to 50 % patients), hirsutism, etc.

Hexamidine (primidone) is less active anticonvulsant than phenobarbital and diphenine; but its toxicity is also less. Drowsiness, dizziness, headache, nausea, and ataxia can occur during first days of the drug intake. Long-time intake of hexamidine can cause deficiency of folic acid.

Carbamazepine is used to treat all forms of epilepsy. The drug is derivative of dibenzazepine. Its mechanism of action is associated with blockage of sodium channels in epileptic focus. Carbamazepine significantly reduces activity of Na^+, K^+-ATPase and concentration of cAMP. Carbamazepine exhibits favorable influence upon psyche. Patients, taking carbamazepine, become more sociable; their interest in the word is increased, depression and hypochondria are reduced, and mood improves. Side effects of carbamazepine are dispepsy, headache, drowsiness, allergic reactions, leukopenia, thrombocytopenia, agranulocytosis, and hepatitis.

Clonazepam is benzodiazepine derivative. The drug is taken orally. Clonazepam is readily absorbed from gastrointestinal tract, easily penetrates through the placental barrier and in the mother's milk. The drug exhibits tranquilizing and anticonvulsive effects. Its mechanism of action is associated with activation of GABA-ergic

receptors in epileptic focus. Also, the drug interrupts dissemination of pathological impulses. Clonazepam is used to cessate epilepsy attacks in children and adults, to treat petit mal epilepsy and myoclonus epilepsy. Side effects of clonazepam are ataxia, depression, aggressiveness, increased fatigue, nausea, etc. The drug causes psychical and physical dependence.

Ethosuximide is a drug of choice to treat petit mal epilepsy. The drug is easily absorbed from gastrointestinal tract and readily penetrates through the blood-brain barrier and other histohematological barriers. Ethosuximide blocks GABA-transferase in the central nervous system that leads to accumulation of GABA and reduction of convulsive activity of neurons. Besides, ethosuximide blocks T-type calcium channels. Side effects of ethosuximide are gastrointestinal disorders, headache, dizziness, agranulocytosis, and violation of renal function.

Sodium valproate is used in the treatment for petit mal epilepsy, psychomotor seizures, and grand mal epilepsy. The drug has complex mechanism of action. Sodium valproate blocks GABA-transaminase (4-aminobutyrate transaminase) and simultaneously activates glutamate dehydrohenase. The last enzyme participates in the synthesis of GABA. Besides, sodium valproate blocks sodium channels and calcium channels of T-type. The drug improves mood of patients, reduces depression and fear. Side effects of sodium valproate include nausea, drowsiness, hair loss, etc.

Lamotrigine is used in the treatment of different forms of epilepsy. Its mechanism of action is associated with reduction of glutamate release from presynaptic nervous endings. Also, the drug blocks sodium channels. Lamotrigine is completely absorbed from gastrointestinal tract. The drug has long duration of action. Its side effects are dizziness, drowsiness, ataxia, nausea, allergic reactions, etc.

Drugs for Treatment of Muscular Spasticity

Increased reflectory excitability of segmental apparatus plays an important role in the development of muscular spasticity. A state of brainstem and interneurons (internuncial or relay neurons) of spinal cord is an important for formation of this pathology. Therefore, drugs reducing excitability of intercalative neurons and inhibiting spinal reflexes exhibit therapeutic effect at muscular spasticity. These drugs are central myorelaxants: *tolperizosone (Mydocalm), tizanidine (Sirdalud),* GABA derivative *baclofen,* and benzodiazepine derivatives (*clonazepam, diazepam, phenazepam,* etc.).

Tolperizosone (Mydocalm) influences mainly interneurons of brainstem (descending facilitating system). *Tizanidine*, *baclofen*, and benzodiazepines inhibit reflexes mainly at the level of spinal cord. Drugs eliminate symptoms of spasticity. High doses of these drugs decrease the tone of skeletal muscles. Unlike peripheral myorelaxants, centrally acting drugs do not cause total relaxation of skeletal muscles, weakly inhibit arbitrary movements, and do not stop breathing. Mydocalm, tizanidine, and baclofen exhibit moderate sedative and hypnotic effects.

Central myorelaxants are used to treat spasticity of skeletal muscles of different origin, intoxication by strychnine, tetanus, operations on limbs (reposition of bone fractures and reversal of dislocations), abdominal surgery with the use of local anaesthetics, pathologically increased tone of skeletal muscles in patients suffering from diseases of the musculoskeletal system, neuralgias, and some gynecological diseases.

Antiparkinsonic Drugs

Antiparkinsonic drugs are used to treat Parkinson disease, symptomatic parkinsonism, and other diseases caused by disbalance of mediators of extrapyramidal system.

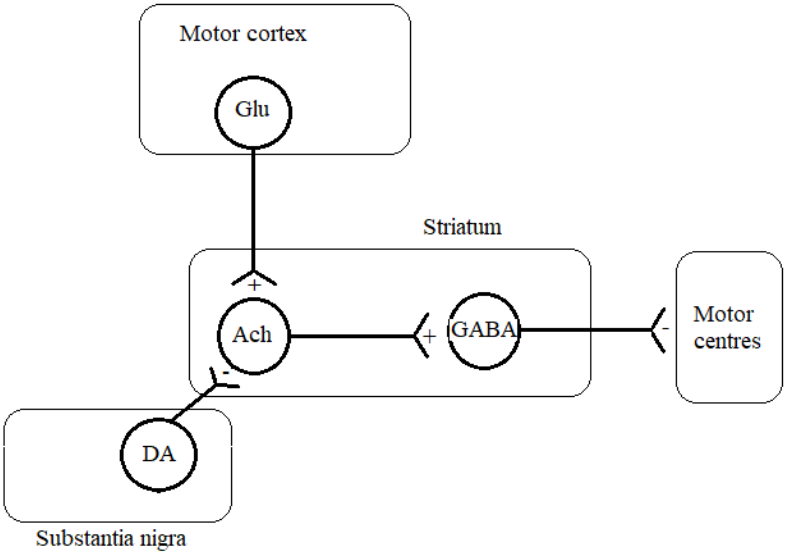

Figure 12 – Scheme of the influence of the extrapyramidal system on the motor activity:

Glu – glutamate-ergic neuron; Ach – cholinergic neuton;
DA – dopaminergic neuron; GABA – GABA-ergic neuron;
"+" – stimulative influence; "-" – inhibitory influence

Parkinson disease was firstly described by physician James Parkinson in 1817. At this disease, the concentration of dopamine in extrapyramidal system is sharply decreased that results in reduction of its inhibitory influence upon cholinergic neurons participating in regulation of activity of spinal motor neurons. An increased activity of cholinergic and glutamatergic neurons leads to appearance of rigidity (sharply increased muscular tone), tremor, and hypokinesia (stiffness of movements). Gait and posture change. Also, psychical and mental disorders develop gradually. Therapy of parkinsonism is directed to

restoration of mediators disbalance: activation of dopaminergic neurons and/or inhibition of excessive activity of cholinergic and glutamatergic neurons of extrapyramidal system.

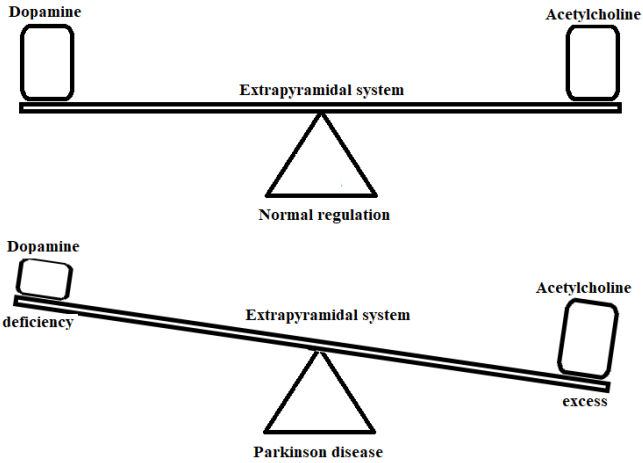

Figure 13 – An imbalance between dopamine and acetylcholine levels leads to Parkinson's disease

Therefore, antiparkinsonic drugs are classified as follows:

1. Drugs improving dopaminergic activity.

1.1. Drugs which restore dopamine level: *levodopa* and combined drugs – *sinemet, nacom, madopar, tolcapone.*

1.2. Dopaminergic receptor agonists: *bromocriptine, ropinirole.*

1.3. Monoamine oxidase B (MAO-B) inhibitors: *selegiline.*

2. Drugs inhibiting glutamatergic influence: *amantadine.*

3. Anticholinergic agents: *cyclodol (trihexyphenidyl), biperiden, benztropine, tropacinum.*

The therapy of parkinsonism is pathogenetic.

At parkinsonism, dopamine level in basal ganglia is reduced. Therefore, drugs which increase its level in the central nervous system are used to treat parkinsonism. Dopamine itself is not used as medicine because it poorly penetrates through the blood-brain barrier. Instead

dopamine, its precursor levodopa (dioxyphenylalanine) is used in medicine. Levodopa easily penetrates the central nervous system, decarboxylated and transformed to dopamine that restores mediator amount and provides therapeutic effect of levodopa.

Levodopa is taken orally. Bioavailability of levodopa taken orally is about 20–30 %. Maximal blood concentration of levodopa is observed in 2–3 hours after the drug intake. Initial therapeutic effect is observed in a week. Maximal effect develops in a month after the start of therapy. There are several pathways of levodopa metabolism in the body: decarboxylation, transamination, methylation, and conjugation. It should be noticed that speed of levodopa inactivation depends on vitamin B_6 concentration because this vitamin is cofactor of enzyme inactivating levodopa.

Peripheral DOPA-decarboxylase transforms a part of the taken levodopa in dopamine that leads to some side effects of the drug: nausea, vomiting, disorders of the heart rate, and ortostatic hypotension. For reduction of these complications, levodopa is combined with inhibitors of peripheral DOPA-decarboxylase which do not penetrate the central nervous system. Thus, *Nacom* and *Sinemet* are combinations of levodopa with *carbidopa*; *Madopar* is a combination of levodopa with another inhibitor of peripheral DOPA-decarboxylase – *benserazide*. Combined drugs are not used to treat patients with diseases of endocrine system, liver, kidneys, heart, and psychosis. Also, these drugs are contraindicated to treat young people under 25 years (bone growth should be completed).

Bromocriptine is agonist of dopaminergic receptors. As a rule, this drug is used together with levodopa.

Another agent of this group – *ropinirole* – stimulates D_2- and D_3-receptors in neostriatum (corpus striatum). Ropinirole is more potent agent than bromocriptine.

Drugs, reducing dopamine inactivation due to the blockage of MAO-B, are used to increase the dopaminergic influence in extrapyramidal system. *Selegiline* (*deprenyl*) is selective irreversible inhibitor of MAO-B.

Amantadine inhibits stimulative glutamatergic influence due to blockage of NMDA-receptors and blocks M-cholinergic receptors. The drug is absorbed from gastrointestinal tract slower than levodopa. Its maximal concentration in blood is observed in 4 hours after the drug intake. Non-metabolized amantadine is slowly excreted by kidneys. Its half-life is about 15 hours. Also, the drug exhibits antiviral activity.

Central cholinoblockering drugs (*cyclodol, biperiden,* etc.) exhibit antiparkinsonic effect owing to blockage of M-cholinergic receptors in membranes of neurons of basal ganglia.

Antiparkinsonic drugs reduce hypokinesia, muscular rigidity, tremor, drooling, and secretion of sweat and sebaceous glands.

These drugs are used to treat Parkinson disease, symptomatic parkinsonism, and extrapyramidal disorders caused by neuroleptics.

Side effects of drugs improving dopaminergic influence include dispepsy, horeathetoid hyperkinesis, headache, postural hypotension, and disorders of the heart rate.

Amantadine can cause dispepsy, weakness, headache, and insomnia.

Side effects of cholinergic antagonists are associated with blockage of peripheral M-cholinoceptors and include dry mouth, disorders of accommodation, elevation of intraocular pressure, tachycardia, constipation, etc.

Table 17 – Drugs for prescription

Drug name (Latin)	**Single dose and mode of administration**	**Drug product**
1	2	3
Lamotrigine	Orally 0.05–0.2 g 1 time a day	Tablets 0.05, 0.1 or 0.2 g
Dipheninum	Orally 0.117 g 3 times a day	Tablets 0.117 g
Carbamazepinum	Orally 0.2–0.4 g 1–2 times a day	Tablets 0.1, 0.2 or 0.4 g

Continuation of the table 17

1	2	3
Phenobarbitalum	Orally 0.05 g 1–2 times a day	Tablets 0.05 or 0.1 g
Ethosuximidum	Orally 0.25 g 2–3 times a day	Capsules 0.25 g
Clonazepamum	Orally 0.001–0.002 g 3–4 times a day	Tablets 0.001 or 0.002 g
Levodopa	Orally 0.25–1.0 g 3 times a day	Tablets 0.25 or 0.5 g; capsules 0.25 or 0.5 g
Midantanum	Orally 0.1–0.2 g 2–4 times a day	Coated tablets 0.1 g
Nacom	1 tablet 1–4 times a day	Tablets containing 0.25 g of levodopa and 0.025 g of carbidopa
Cyclodolum	Orally 0.001–0.005 g 2–3 times a day	Tablets 0.001, 0.002 or 0.005 g

Step 1. Tasks for Self-Control
Anticonvulsants

1. A doctor discusses with colleagues the use of a new antiepileptic drug – sodium valproate. What is the mechanism of action of this drug?

A. Inhibition of MAO.

B. Inhibition of GABA-transferase activity.

C. Stimulation of GABA-transferase activity.

D. Inhibition of Ca^{2+}-dependent ATP-ase activity.

E. Stimulation of Ca^{2+}-dependent ATP-ase activity.

2. A patient complains of muscles rigidity, constant tremor of hands, and slowing down of motions. In the result of examination, the doctor determined the diagnosis of Parkinson's disease. Choose the rational drug for treatment of this patient.

A. Ethosuximide.

B. Diphenine (phenytoin).

C. Phenobarbital.

D. Levodopa.

E. Sibazon (diazepam).

3. A 58-year-old male complains of Parkinson's disease. The patient also suffers from glaucoma. What drug should be prescribed to the patient?

A. Cyclodol (trihexyphenidyl).

B. Levodopa.

C. Phenobarbital.

D. Diphenine.

E. Ethosuximide.

4. Tremor and disturbances of coordination are observed in a 68-year-old male. His diagnosis is Parkinson's disease. What drug should be prescribed to the patient?

A. Ethosuximide.

B. Phenobarbital.

C. Diphenine (phenytoin).

D. Levodopa.

E. Finlepsin.

5. Levodopa was prescribed to a 70-year-old male, who suffers from Parkinson's disease. In a week the condition of the patient significantly improved. What is the mechanism of levodopa action?

A. Activation of enkephalinergic system.

B. Suppression of cholinergic system.

C. Suppression of histaminergic system.

D. Suppression of serotoninergic system.

E. Activation of dopaminergic system.

6. Convulsions with the loss of consciousness appear periodically in a 5-year-old child. The doctor has diagnosed epilepsy (grand mal). What drug should be prescribed in this case?

A. Phenobarbital.

B. Amizylum.

C. Cyclodol (trihexyphenidyl).

D. Ethosuximide.

E. Levodopa.

7. A patient, who suffers from grand mal with loss of consciousness, amnesia, and spontaneous outflow of urine, was treated in a neurological unit. What drug should be prescribed to him?

A. Levodopa.

B. Phenobarbital.

C. Ethosuximide.

D. Clonazepam.

E. Trimethine.

8. A patient suffers from posttraumatic epilepsy (grand mal). What drug should be prescribed to the patient?

A. Midantanum (amantadine).

B. Cyclodol.

C. Levodopa.

D. Teturamum (disulfiram).

E. Phenobarbital.

9. A patient with epilepsy accepted phenobarbital in a daily dose 0.4 g for a long time. Recently the attacks of epilepsy became more frequent. What is the reason of the patient's condition deterioration?

A. Inhibition of glycolysis.

B. Inhibition of microsomal hepatic enzymes.

C. Activation of lipolysis.

D. Induction of microsomal hepatic enzymes.

E. Activation of gluconeogenesis.

10. A 42-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 250 mg/dl. Hospital records show a prior hospitalization for alcohol related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A. Phenytoin.

B. Diazepam.

C. Pentobarbital.

D. None.

E. Phenobarbital.

11. A 58-year-old man came to a doctor with complains of trembling, akinesia, muscular rigidity. The doctor has diagnosed

Parkinson's disease. This patient also suffers from glaucoma. What drug is it necessary to prescribe?

A. Methacinum.

B. Levodopa.

C. Cyclodol.

D. Atropine sulfate.

E. Scopolamine hydrobromide.

12. A 70-year-old man with Parkinson's disease has been appointed a levodopa drug. In a week the condition of the patient has considerably improved. What is the mechanism of this drug action?

A. Activation of opiate receptors.

B. Inhibition of cholinergic receptors.

C. Inhibition of histaminic receptors.

D. Inhibition of serotoninergic receptors.

E. Activation of dopamine receptors.

13. A 5-year-old child periodically experiences convulsive attacks with loss of consciousness. A doctor diagnosed epilepsy. What drug is recommended to this child?

A. Amizylum.

B. Cyclodol.

C. Ethosuximide.

D. Levodopa.

E. Phenobarbital.

14. A drug, the derivative of dipropylacetic acid which depresses GABA-transferase, raising the content of GABA in the tissues of the brain, reduces the excitability and readiness for convulsions of motor zones of the brain, has been prescribed to a patient with epilepsy. It is applied at all forms of epilepsy. What is this drug?

A. Sodium bromide.

B. Diazepam.

C. Sodium valproate.

D. Tinctura Valerianae.

E. Reserpine.

15. The significant improvement of motor performance is observed in a patient with Parkinson's disease after the prolonged

using of drug which is transformed into dopamine in the result of decarboxylation. What drug does the patient use?

A. Aminazine.

B. Naloxone.

C. Celecoxib.

D. Droperidol.

E. Levodopa.

16. The prescribing of levodopa to a 60-year-old patient with Parkinson's disease rapidly improves his condition. What is the mechanism of the drug action?

A. Activation of dopamine synthesis.

B. Stimulation of M-cholinoceptors.

C. Blockade of M-cholinoceptors.

D. Stimulation of dopaminergic receptors.

E. Anticholinesterase action.

17. A patient has appealed to a doctor with complaints of muscles rigidity, tremor, and restraint of movements. In the result of examination, the doctor made diagnosis of Parkinson's disease. Make correct choice of a drug.

A. Ethosuximide.

B. Diphenine.

C. Phenobarbital.

D. Levodopa.

E. Sibazon.

18. A patient suffers from repeating attacks of epileptic convulsions with loss of consciousness. What group of drugs is used first for seizures elimination in this case?

A. Sedative drugs.

B. Neuroleptics.

C. Miorelaxants.

D. Tranquilizers.

E. Analeptics.

19. A patient consulted a physician about muscle rigidity, constrained movements, permanent arm tremor. The patient was

diagnosed with Parkinson's disease. What drug should be administered?

A. Levodopa.
B. Ethosuximide.
C. Diazepam.
D. Phenytoin.
E. Phenobarbital.

PSYCHOTROPIC DRUGS

Psychotropic drugs selectively influence emotions, behavior, and cognitive sphere. These drugs are used to treat psychical disorders and borderline states. According to the WHO, 1/3 of adults in developed countries take psychotropic drugs. Psychotropic drugs are classified as follows:

– neuroleptics (antipsychotic drugs);
– tranquilizers (anxiolytics);
– sedative drugs;
– antidepressants;
– lithium salts;
– psychostimulants;
– nootropics (smart drugs or cognitive enhancers);
– adaptogens;
– psychodisleptics (hallucinogens).

In general, the mechanisms of action of psychotropic drugs are associated with their ability to influence neurotransmission in the central nervous system. These drugs change synthesis, release, deposition, and inactivation of mediators.

There are the following mediators in the central nervous system: amino acids (glutamic and aspartic acids, GABA, and glycin), monoamines (dopamine, noradrenaline, and serotonin), acetylcholine, peptides (opioid peptides, substance P, etc.), nitrous oxide, etc.

Amino acids and acetylcholine are mediators which implement "fast signalization". Glutamic acid is the main stimulating mediator in the central nervous system. GABA and glycin are the main inhibiting

mediators. Acetylcholine exhibits mainly the function of an excitating mediator. Its main effects are due to excitation of M-cholinergic receptors, the high quantity of which is in basal nuclei. These receptors participate in a transmission of ascending cortical stimules and in the processes of memory formation.

Besides the system of "fast signalization", there is a system of "slow signalization" in the brain. Its main mediators are monoamines. The function of central monoaminergic system is completely unknown. But its disorders pay an important role in pathogenesis of some diseases, such as parkinsonism, depression, schizophrenia, migraine, etc.

Antipsychotic Drugs (Neuroleptics)

Neuroleptics are drugs which inhibit central nervous system and eliminate or reduce disorders of perception and intellection and decrease productive symptoms of psychosis (hallucinations, delirium, and mania). Nowadays, these drugs are the main agents in the treatment for psychosis and schizophrenia.

Neuroleptics are divided into typical and atypical drugs. Typical neuroleptics often impair functions of the extrapyramidal system (cause parkinsonism and other motor disorders). Atypical neuroleptics quite rare cause parkinsonism, and it is less expressed.

1. Typical neuroleptics:

1.1. Phenothiazine derivatives: *aminazine (chlorpromazine), triftazine, phthorphenazine, levomepromazine (Tisercin), thioproperazine (Majeptil),* and *frenolon.*

1.2. Thioxanthene derivatives: *chlorprothixene* and *thiothixene.*

1.3. Butyrophenone derivatives: *haloperidol, droperidol,* and *trifluperidol (Trisedyl).*

1.4. Difluoro diphenylbutane derivatives: *pimozide (Orap), fluspirilene (Imap),* and *penfluridol (Semap).*

1.5. Alkaloids of Rauwolfia: *reserpine.*

2. Atypical neuroleptics:

2.1. Benzamide derivatives: *sulpiride.*

2.2. Dibenzodiazepine derivatives: *clozapine*.

2.3. Dopaminergic receptor agonists: *aripiprazole*.

Derivatives of phenothiazine, butyrophenone, and difluoro diphenylbutane are most commonly used in psychiatric practice. Drugs of other groups are of secondary importance.

The mechanism of action of neuroleptics is associated with their ability to block D_2-dopaminergic, α-adrenergic, M-cholinergic, H_1-histaminergic, and serotoninergic receptors in the central nervous system. The main factor, determining their psychotropic effect, is ability of drugs to block dopaminergic and α-adrenergic receptors. The action of neuroleptics directs mainly to the three brain structures: the ascending activating part of reticular formation (controls attention, excitation, and anxiety), limbic system (which is responsible for emotions), and hypothalamus (performs regulation of endocrine and vegetative nervous systems). These structures modify cortex activity by means of ascending axons of their neurons.

There is evidence that psychical disorders, typical for schizophrenia, are associated with hyperfunction of dopaminergic system.

A therapy with neuroleptics is accompanied by reduction of excessive activity of catecholergic system and normalization of pathological changes in the modulating systems of the brain.

On the synaptic level, there are the following components in the mechanism of action of neuroleptics:

– competitive blockage of postsynaptic receptors;

– inhibition of mediator release into synaptic cleft and reduction of its reuptake by presynaptic endings that leads to the increased enzymatic degradation of mediator;

– blockage of presynaptic receptors which regulate intensivity of synaptic transmission by means of positive feedback.

Pharmacological effects of neuroleptics are listed below.

1. Antipsychotic effect is due to the blockage of dopaminergic and serotoninergic receptors. This effect is manifested by elimination of stable pathological personality changes, antisocial traits of behavior, delirium, halucinations, and by an increased interest in the

environment, amplification of motivation and initiative. Besides, blockage of dopaminergic receptors in extrapyramidal system is accompanied by extrapyramidal disorders (drug-induced parkinsonism).

2. Sedative effect develops owing to the blockage of α-adrenergic, M-cholinergic, and H_1-histaminergic receptors in the central nervous system, mainly in the ascending part of reticular formation. The main manifestations of this effect are elimination of psychomotor excitement, flaccidity, drowsiness, impairment of mental function, apathy, collaptoid reactions, and reduced interest in the environment.

Expressivity of sedative and antipsychotic effects of different drugs is different. Therefore, neuroleptics are divided into two groups:

I. Neuroleptics with a marked sedative effect that dominates over antipsychotic effect: *aminazine (chlorpromazine), droperidol, levomepromazine (Tisercin),* etc. These drugs are used to cessate psychosis with general excitation, anxiety, and aggression.

II. Neuroleptics with a marked antipsychotic effect: *thioproperazine (Majeptil), trifluperidol (Trisedyl), fluspirilene (Imap), haloperidol,* etc. These drugs are used to treat patients with stable psychotic symptoms (hallucinations, delirium, and mania).

3. Antiemetic effect of neuroleptics is associated with blockage of D_2-dopaminergic receptors of a trigger zone, located in the rhomboid fossa of the fourth ventricle of the brain. Neuroleptics are effective drugs in the treatment for vomiting of the central origin that develops due to intoxications, radiation sickness, toxemia of pregnancy, etc.

4. Reduction of muscular tone and motor activity (myorelaxating effect). Neuroleptics provide relaxation of skeletal muscles by means of blockage of α-adrenergic receptors of the descending part of reticular formation.

5. Potentiation of general anaesthesia and analgesia. This effect of neuroleptics is due to the blockage of α-adrenergic, M-cholinergic, and H_1-histaminergic receptors of reticular formation that leads to the decrease of its influence upon the cortex. Droperidol exhibits the most

marked ability to potentiate anaesthesia and analgesia. This drug is used to prevent cardiogenic, traumatic, and burn shock. Also, droperidol is used for neuroleptanalgesia.

6. Hypothermic effect (lowering of body temperature). Body temperature is lowered due to the increase of heat emission and decrease of heat production. Increased heat emission is associated with vasodilation due to the blockage of peripheral α-adrenergic receptors and inhibition of hypothalamic centre of termoregulation. The decreased heat production is due to inhibition of oxidating processes in tissues. Hypotermic effect of neuroleptics is fundamentally different from the antipyretic effect of nonsteroid anti-inflammatory drugs that is expressed only at fever. Aminazine is most commonly used for this purpose. This drug is a component of lytic mixtures which are used in surgery for artificial cooling.

7. The decrease of blood pressure is a result of blockage of peripheral α-adrenergic receptors, inhibition of vasomotor centre, and direct antispasmodic action of neuroleptics.

8. Neuroleptics inhibit negative emotions (anxiety, fear, and general excitation).

9. Antiallergic effect is associated with the blockage of H_1-histaminergic receptors and is most expressed in promethazine (Pipolphen, Diprazine).

10. M-cholinolytic effect is manifested by hyposecretion of salivary, bronchial, and digestive glands.

Aminazin is administered parenterally or taken orally. Its duration of action is 6 hours. Only 30 % of the taken dose is absorbed from gastrointestinal tract. Aminasine is metabolized in the liver. The drug and its metabolites are excreted by kidneys and intestine during several days.

Haloperidol has a faster onset of action. Its maximal concentration is accumulated in the blood in 2–6 hours after an oral intake and is kept at a high level up to 3 days.

Clozapine has a fast but short-time effect. Its maximal concentration in the blood is observed in 2 hours after an intake. The main part of the taken dose is excreted from the body during a day.

Aripiprazole is an atypical neuroleptic, a partial agonist of D_2-dopaminergic and 5-HT_{1A}-serotoninergic receptors, and an antagonist of 5-HT_{2A}-serotoninergic receptors. The drug is used in to treat schizophrenia and bipolar disorder.

Aripiprazole is taken orally and administered intramuscularly. The dose for oral intake is 10–15 mg; the drug is taken once a day. Its side effects are tardive dyskinesia, constipation, dizziness, vomiting, weight gain, sleepiness. It should be noted, that the drug can cause such severe complication as neuroleptic malignant syndrome.

There are the following indications for the use of neuroleptics:

1. Schizophrenia, bipolar disorder (manic depression) in a phase of mania, psychical disorders in patients with organic damages of the brain, epilepsy, etc.

2. Aggravation of endogenous psychosis with hallucinations, delirium, mania, and aggression.

3. Acute psychical disorders with psychomotor excitement and reactive psychosis at traumas, infections, etc.

4. Delirium and withdrawal syndrome.

5. Vegetoneurosis at the ischemic heart disease, ulcer disease of the stomach, at climacteric period, and hypertensive crisis with encephalopathy.

6. Nausea and vomiting of a central origin and persistent hiccups.

7. Traumatic and burn shocks (drugs are administered intravenously drop-by-drop for improvement of blood perfusion of internal organs).

8. Neuroleptanalgesia (a type of general anaesthesia that is used during operations, severe burns, traumas, etc.).

Therapy with neuroleptics may be accompanied by the following side effects:

1. Tachycardia, drop of blood pressure (up to ortostatic collapse), involuntary contractions of facial muscles and muscles of upper limbs are observed during 10–12 hours after a drug intake.

2. Short-time transient pain, parastesia, dyspepsy, temporary hypo- or hypertermia, disorders of accommodation, hypersalivation or dry mouth can occur in 2–3 weeks of a regular drug intake.

3. Extrapyramidal disorders (Parkinsonism, dyskinesia, and muscular dystony) occur due to the blockage of inhibitinhg dopaminergic influence of substantia nigra upon the globus pallidus and caudate nucleus that leads to the increase of facilitating influence upon motoneurons of the spinal cord. Muscular rigidity, tremor and other extrapyramidal disorders occur. This patology develops in 25–38 % of patients who were treated by neuroleptics. Extrapyramidal disorders are less expressed in case of the therapy with drugs which block dopaminergic receptors only in a limbic system and cortex, and exhibit additional M-cholinolytic properties (e. g. clozapine).

4. Hepatotoxicity is typical for phenothiazine derivatives. Jaundice develops owing to cholestasis and focal lesions of hepatic parenchyma.

5. Allergic reactions: skin rashes, itching, eczema, and angioedema.

6. Blood dyscrasias: leukopenia, agranulocytosis, increase of erythrocyte sedimentation rate (ESR). Erythropenia and dysproteinemia are sometimes observed.

7. Corneal and lens opacities are due to the pigment metabolism disorder owing to the increase of melanostimulating hormone secretion.

8. Endocrine disorders: an increase of secretion of melanostimulating hormone and prolactine and decrease of secretion of somatotropin, adrenocorticotropin, tyrotropin, gonadotropins, oxytocin, and vasopressin. Due to this, galactorhea and amenorrhea develop in women and gynecomasty and impotention develop in men.

9. Sudden cessation of the therapy with phenothiazine derivatives is accompanied by the withdrawal syndrome occurring in 30 % of patients. Its symptoms include nausea, vomiting, and aggravation of the mental condition.

10. As a result of idiosyncrasy, neuroleptic malignant syndrome occurs in about 1 % of patients. Rigidity, sharp increase of the body temperature, impaired consciousness, and cardiovascular disorders are observed in these patients. About 10–20 % of patients with neuroleptic

malignant syndrome die. Diazepam, bromocriptine, and dantrolene are used to treat neuroleptic malignant syndrome.

Long-time therapy with neuroleptics can lead to tolerance. Drug dependence to neuroleptics does not develop.

Antidepressants

Antidepressants are the drugs with the different chemical structure used to treat psychical depressions (major depressive disorders) and minor depressive disorders. Nowadays, 3–5 % of population in the word suffer from depressions.

Antidepressants are classified as follows:

1. Drugs inhibiting neuronal reuptake of monoamines (noradrenaline and serotonin).

1.1. Drugs with nonselective action which block neuronal reuptake of both serotonin and noradrenaline: *imipramine (imizinum), pipofezine (Azafen), fluacizine (Phtorazisin), amitriptyline*.

1.2. Selective serotonin reuptake inhibitors: *fluoxetine, fluvoxamine, sertraline.*

1.3. Selective inhibitors of the neuronal reuptake of noradrenaline: *maprotiline.*

2. MAO inhibitors.

2.1. Nonselective and irreversible MAO inhibitors (block both MAO-A and MAO-B): *nialamide, transaminum.*

2.2. Selective and reversible inhibitors of MAO-A: *moclobemide, pyrasidole, incazanum.*

All antidepressants influence limbic system. Drugs inhibiting neuronal reuptake of monoamines slow down reuptake of noradrenaline, dopamine, and serotonin. Besides, these drugs sensitize postsynaptic receptors to corresponding mediators and block presynaptic α_2-adrenergic receptors which decrease mediator release by means of negative feedback. As a result, mediator concentration in a synaptic cleft is increased providing antidepressive and antiasthenic effects.

The mechanism of action of MAO inhibitors is associated with suppression of MAO activity. MAO is in mitochondria of adrenergic and serotoninergic nervous endings and in inner organs (liver, small intestine, etc.). MAO inhibition leads to slowing down the inactivation of monoamines (serotonin, noradrenaline, and dopamine), accompanied by enhanced release of these mediators into the synaptic cleft. Nonselective inhibitors of MAO-A and MAO-B block these enzymes irreversibly, therefore both activity and toxicity of these drugs are higher than those of other antidepressants.

Pharmacological effects of antidepressants are given below.

1. These drugs improve mood and eliminate melancholy, depression, feeling of hopeless, and suicidal thoughts.

2. Some tricyclic antidepressants (e. g., amitriptyline) exhibit also sedative and tranquilizing effects associated with their ability to block M-cholinergic receptors. These effects are manifested by reduction of anxiety and fear. Such drug as fluoxetine lacks these effects but exhibits psychostimulating action.

3. MAO inhibitors exhibit additional psychostimulatory effect associated with activation of noradrenergic transmission in the central nervous system. These drugs restore initiative and motivation and decrease mental and physical tiredness.

4. Some drugs (e. g., imipramine) exhibit peripheral antihistaminic, M-cholinoblocking, and antispasmodic effects.

Antidepressants are used to treat major depressive disorders, minor depressive disorders, neurasthenia with elements of depression, neurosis, enuresis, sleep disorders based on depression, and obsessive–compulsive disorder.

As a rule, antidepressants are prescribed 1–2 times a day. Therapeutic effect is observed in 7–14 days. The effect of drugs inhibiting neuronal reuptake of serotonin (fluoxetine, sertraline, etc.) develops more slowly (in 1–4 weeks). Course of treatment is individual and lasts from 1 to 6 months. It should be noticed that simultaneous treatment with MAO inhibitors and tricyclic antidepressants is unacceptable because it can provoke severe complications up to the patient death.

Therapy with tricyclic antidepressants can cause hypotension, cardiac arrhythmias, and disturbances of cardiac conduction. MAO inhibitors cause hypertension, tachycardia, and mental agitation. Sometimes, allergic reactions, jaundice, hematopoietic disorders are possible. Due to the ability to block M-cholinergic receptors, tricyclic antidepressants can cause dry mouth, urinary retention, constipation, and aggravation of glaucoma.

Nonselective MAO inhibitors can provoke the so-called "cheese syndrome". Its mechanism is associated with the ability of drugs to increase effects of biogenic vasoconstricting monoamines (tyramine and phenylethylamine) which are contained in such foodstuffs as cheese, cream, beans, coffee, beer, wine, etc. In normal conditions, these monoamines are inactivated by MAO of the liver and small intestine. Simultaneous use of nonselective MAO inhibitors and eating of the mentioned foodstuffs increase concentration of tyramine and phenylethylamine that leads to hypertension. Selective inhibitors of MAO-A have less duration of action and the possibility of hypertensive crisis is less.

Due to a psychostimulatory effect, MAO inhibitors can cause euphoria and insomnia.

Drugs for Mania Treatment

Salts of lithium *(lithium carbonate* and *lithium oxybutirate)* are used to treat mania. These drugs have the narrow use in medicine because they are able to prevent or eliminate maniacal manifestations of psychoses (euphoria, carelessness, excessive optimism, maniacal ideas, verbal and motor excitement, etc.).

The mechanism of action of lithium is not clear enough. Lithium ions can replace sodium ions in the cells. Lithium ions enter inside of cells through fast sodium channels and partly replace sodium. But lithium ions are slowly removed from the cells, influencing the processes of membrane depolarization. Besides, lithium decreases the release of noradrenaline and dopamine in the synapses. Also, lithium influences secondary messendgers (inositol and diacylglycerol) which participate in transmission of sygnals from α-adrenergic and M-cholinergic receptors. There are evidences that lithium blocks

adenylyl cyclase and decreases intracellular synthesis of cAMP. The mentioned mechanisms normalize processes of depolarization and repolarization of cellular membranes, synthesis and release of mediators, conjugation of the receptor excitation with changes of cellular functions, etc.

Long-time intake of lithium salts leads to the loss of sodium, magnesium, and water and accumulation of calcium in a human body.

Lithium salts are readily absorbed from gastrointestinal tract and slowly penetrate the blood-brain barrier. These drugs are excreted by kidneys.

Lithium carbonate is the most commonly used preparation of lithium. The drug effect develops in 2–6 weeks. The duration of therapeutic course is at least 2 years. The duration of remission period is 10–12 years and more. The success of treatment depends on compliance with accuracy in the dosing regimen of the drug. Daily doses are individual and fluctuate from 0.6 to 1.6 g. It is necessary to maintain the stable concentration of lithium in the blood and in the brain. Lithium concentration in the plasma should be within the range 0.6–1 meq/liter.

The therapeutic indications for lithium salts are prevention and treatment of mania.

Side effects of lithium salts are dyspepsy, tremor, increased tiredness, drowsiness, headache, thyroid dysfunction, diarrhea, polyuria, thirst, renal disorders, and imbalance of electrolites. It should be noticed that an insignificant amount of lithium is excreted by mammary glands.

Poisoning by lithium salts is possible due to its overdose or reduced amount of sodium in the body (salt-free diet, therapy with diuretics, etc.). The manifestations of poisoning are vomiting, diarrhea, ataxia, convulsions, etc. In severe cases, coma and death are possible. Treatment of lithium poisoning is directed to fast elimination of lithium from the body. Osmotic diuretics (mannitol) and sodium hydrocarbonate are prescribed to a patient for this purpose. In severe cases, hemodialysis is used.

Table 18 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Aminazinum	Orally 0.025–0.05 g 1–3 times a day; intramuscularly 0.01 g 1–3 times a day; intravenously 1–2 ml of 2.5 % solution in 20 ml of 40 % glucose solution (at acute psycho-motor excitement)	Dragee 0.025, 0.05 or 0.1 g; ampoules 1, 2, 5 or 10 ml of 2.5 % solution
Triftazinum	Orally 0.005–0.01 g once a day; intramuscularly 0.001–0.002 g once a day	Tablets 0.001, 0.005 or 0.01 g; ampoules 1 ml of 0.2 % solution
Haloperidolum	Orally 0.0015–0.005 g 3 times a day; intramuscularly 0.002–0.005 g	Tablets 0.0015 or 0.005 g; ampoules 1 ml of 0.5 % solution
Droperidolum	Intramuscularly or intravenously 0.0025–0.005 g	Ampoules 5 or 10 ml of 0.25 % solution
Imizinum	Orally 0.025–0.05 g 1–3 times a day; intramuscularly 0.025 g 1–3 times per day	Tablets 0.025 g; ampoules 2 ml of 1.25 % solution
Amitriptylinum	Orally 0.025–0.05 g 3–4 times a day; intramuscularly or intravenously 0.025–0.04 g 3–4 times per day	Tablets 0.025 g; ampoules 2 ml of 1 % solution
Lithii carbonas	Orally 0.3–0.6 g	Tablets 0.3 g

Step 1. Tasks for Self-Control
Antipsychotic Drugs (Neuroleptics), Antidepressants, and Drugs for Mania Treatment

1. A patient was treated medically for psychosis for 2 weeks. The patient's condition improved but rigidity, tremor, and hypokinesia developed. Which of the following drugs can cause such complications?

A. Sydnocarb.

B. Imipramine.

C. Aminazine.

D. Chlordiazepoxide.

E. Diphenine.

2. To eliminate delirium and hallucinations in a patient with schizophrenia a doctor used aminazine. What is the mechanism of antipsychotic action of the drug?

A. Blockade of neuronal reuptake of catecholamines.

B. Stimulation of adrenergic and dopaminergic processes in the CNS.

C. Blockade of adrenergic and dopaminergic processes in the CNS.

D. Stimulation of cholinergic processes in the CNS.

E. Blockade of cholinergic processes in the CNS.

3. A patient with manic-depressive psychosis and manifestations of depression complains of anxiety and fear. What antidepressant with accompanying psychosedative effect is it necessary to prescribe?

A. Amitriptyline.

B. Phenazepam.

C. Imizinum (imipramine).

D. Sydnocarb.

E. Nialamide.

4. A drug shows a strong, fast, but not long-term neuroleptic action. It potentiates the action of analgesic, soporific agents, alcohol. It has anti-shock and antiemetic action. It belongs to butyrophenone derivatives. What is this drug?

A. Sulpiride.

B. Triftazine.

C. Aminazine.

D. Clozapine (azaleprtin).

E. Droperidol.

5. A patient developed symptoms of medicinal parkinsonism after psychosis treatment in a mental hospital. What drug had been used for his treatment?

A. Nialamide.

B. Mezapam.

C. Sodium bromide.

D. Lithium carbonate.

E. Aminazine.

6. Acute heart attack is accompanied by retrosternal pain. Ineffectiveness of preliminary taken drugs has made the doctor to perform neuroleptanalgesia. What neuroleptic is used for this type of anaesthesia?

A. Aminazine.

B. Meterazine (prochlorperazine).

C. Haloperidol.

D. Droperidol.

E. Reserpine.

7. A 38-year-old man suffers from schizophrenia. He has come to a doctor with complaints of coordination and movements disorders, tremor in his hands, drowsiness. The patient has been taking psychotropic drugs for a long period of time. What group of drugs can lead to such complex of symptoms?

A. Adaptogens.

B. Analgesics.

C. Neuroleptics.

D. Antidepressants.

E. Psychomotor stimulants.

8. A patient with maniac-depressive psychosis demonstrates inhibition of mental and motion activity, agitation, depression. What drug should be prescribed to relieve pathological depression?

A. Triftazine.

B. Sydnocarb.

C. Caffeine sodium benzoate.

D. Amitriptyline.

E. Pyracetam.

9. A man is kept under dispensary observation in a psychoneurologic clinic because of chronic alcoholism. Alcohol abuse led to acute psychosis. What drug can be expediently used?

A. Adrenaline.

B. Atropine.

C. Aminazine.

D. Pentamine.

E. Hygronium.

10. What neuroleptic is characterized by the following properties: phenothiazine derivative, blocks postsynaptic dopamine and adrenergic receptors in the CNS, provides a sedative effect on the CNS, prolonged application can induce extrapyramidal abnormalities and neuroleptic syndrome?

A. Haloperidol.

B. Aminazine.

C. Diazepam.

D. Triftazine.

E. Droperidol.

11. A woman tried to commit suicide. A psychiatrist detected a condition of endogenous depression of this patient. What medication is expedient to prescribe to the patient for the course of treatment?

A. Caffeine sodium benzoate.

B. Sydnocarb.

C. Aethymizole.

D. Pyracetam.

E. Amitriptyline.

12. A patient with schizophrenia takes aminazine. Which of the listed pharmacodynamic effects is the basic one in this case?

A. Hypotensive.

B. Antiemetic.

C. Hypothermic.

D. Muscle relaxing.

E. Antipsychotic.

13. An ambulance has delivered a patient, who tried to commit suicide in the condition of severe depression, to a hospital. The diagnosis is depressive psychosis. The drug of which pharmacological group is it necessary to prescribe to the patient?

A. Lithium salts.

B. Antidepressants.

C. Sedatives.

D. Neuroleptics.

E. Tranquilizers.

14. A patient suffering from Parkinson's disease needs additional treatment concerning accompanied pathology. Indicate the group of drugs which can cause aggravation of Parkinson's disease in this patient?

A. Antidepressants.

B. Tranquilizers.

C. Antipsychotic drugs (neuroleptics).

D. Hypnotics.

E. M-cholinoblockers.

15. The first aid brigade has delivered a patient with obvious psychomotor disturbances to a hospital. What drug should be administered to the patient?

A. Bisacodyl.

B. Aminazine.

C. Piracetam.

D. Rifampicin.

E. Heparin.

16. A surgery patient needs neuroleptanaesthesia. What drug is most commonly used for neuroleptanaesthesia together with fentanyl?

A. Fraxiparine.

B. Droperidol.

C. Cholosasum.

D. Salbutamol.

E. Pilocarpine.

17. Pharmacological effects of antidepressants are based upon blocking (inhibiting) the enzyme that acts as a catalyst for the breakdown of biogenic amines noradrenaline and serotonin in the mitochondria of cephalic neurons. What enzyme takes part in this process?

A. Decarboxylase.
B. Lyase.
C. Transaminase.
D. Peptidase.
E. Monoamine oxidase.

Anxiolytic Drugs (Tranquilizers)

Anxiolytics (tranquilizers, ataractics) are the drugs which inhibit the central nervous system and reduce or eliminate negative emotions: internal stress, anxiety and fear. These drugs are effective at neurotic and neurosis-like disorders. First tranquilizer, meprobamate, was synthesized in the USA in 1954. Many other drugs were synthesized later.

Anxiolytics are classified as follows:

1. Agonists of benzodiazepine receptors.

1.1. Long-acting drugs (24–48 hours): *phenazepam, mezapam, chlordiazepoxide (chlozepidum), diazepam (sibazon),* and *flurazepam.*

1.2. Drugs with intermediate duration of action (6–24 hours): *nitrazepam, oxazepam,* and *alprazolam.*

1.3. Short-acting drugs (less than 6 hours): *midazolam* and *triazolam.*

2. Agonists of serotoninergic receptors: *buspirone.*

3. Drugs with different mechanisms of action: *amizylum (Benactyzine), trimetozine (Trioxazine),* and *oxylidine.*

4. Daytime anxiolytics:

– agonists of benzodiazepine receptors: *gidazepam (hydazepam), clorazepate dipotassium (Tranxene), tofisopam (Grandaxin),* and *mezapam;*

– α-adrenoblocking drug: *pyrroxane;*
– nootropic drug: *nootropil;*
– $GABA_B$-receptor agonist: *phenibut.*

Benzodiazepine Derivatives

Benzodiazepine derivatives are drugs with low toxicity; therefore, these drugs are widely used in medicine. These drugs act as agonists of benzodiazepine receptors which are coupled with $GABA_A$-receptors.

$GABA_A$-receptors consist of 5 subunits: two α-, two β-, and one γ-subunit. These subunits penetrate cellular membrane and form the ionic channel for Cl^- ions. There are several pharmacologically important binding sites between the different subunits. For example, the benzodiazepine-binding site (or benzodiazepine receptor) is located between the α- and γ-subunits. The barbiturate binding site is between the β- and α-subunits. This site is activated by barbituric acid derivaives. Between the other pair of β- and α-subunits, is the GABA-binding site.

Interaction of benzodiazepine derivative with the benzodiazepine-binding site leads to allosteric activation of the $GABA_A$-receptor. This results in increase of affinity of GABA for the GABA-binding site. Activation of the GABA-binding site by GABA leads to an increase in the frequency of chlorine channel opening. Increased chlorine entry into neurons causes hyperpolarization of neuronal membranes and inhibition of neuronal activity.

Limbic system (amygdalae and their links with hippocampus) and cortex are most rich in benzodiazepine receptors. Low density of benzodiazepine receptors is in hypothalamus, thalamus, cerebellum, and spinal cord.

The following pharmacological effects are typical for tranquilizers.

1. Anxiolytic effect is associated with influence of drugs upon limbic system. It is manifested by reduction of emotional lability, decrease of psychical stress, anxiety, and fear. Situations, which were estimated earlier as stressful, get quieter and sober estimation. The

critical attitude to events and deeds is completely preserved. Due to anxiolytic effect, vegetative and endocrine frustrations of neurosis are also eliminated.

2. Sedative effect is a result of interaction of benzodiazepines with benzodiazepine receptors in reticular formation. Besides, tranquilizers increase the activity of intracortical inhibitory neurons. Sedative action is manifested by the decrease of reaction on external stimulus, reduction of mental and physical serviceability, and drowsiness. Prescribing these drugs to outpatients whose work requires extra attention (e. g., dispatchers, drivers, installers), is unacceptable.

3. Hypnotic action is a result of influence of benzodiazepines upon limbic system (hippocampus). A decrease of emothional stress also promotes the hypnotic effect. These drugs contribute to falling asleep and increase the total duration of sleep. It should be noticed that benzodiazepines shorten the frequency and general duration of "fast" or desynchronized (REM) sleep. But this undesirable effect is significantly less expressed then those of barbituric acid derivatives.

4. Muscle relaxation is caused by benzodiazepines due to depression of spinal intercalary GABA-ergic neurons. Also, benzodiazepines depress the activity of descending reticular formation. Therefore, benzodiazepines are muscle relaxants with central action.

5. Anticonvulsive action is due to the ability of benzodiazepines to inhibit convulsive discharges in hippocampus which is involved in pathogenesis of the most convulsive reactions.

6. High doses of benzodiazepines cause amnesia due to the marked reduction of cortical activity.

7. Benzodiazepines potentiate the effects of other central nervous system depressants (opioid analgesics, barbiturates, neuroleptics, and general anaesthetics).

There are the following therapeutic indications for benzodiazepines:

1. In psychiatric and neurological practice, benzodiazepines are used to treat so-called borderline states: neuroses, neurotic reactions, psychopaty, etc.

2. Tranquilizers are used in a complex therapy of therapeutic diseases, pathogenesis of which includes neurotic factor: angina pectoris, myocardial infarction, exacerbation of hypertensive disease, ulcer disease, bronchial asthma, etc.

3. Status epilepticus, epilepsy, muscular hypertone which are due to traumas of the central nervous system or insults.

4. Premedication for patients with high psychoemotional lability.

5. Ataralgesia. For this type of general anaesthesia, tranquilizer (diazepam) is administered together with an opioid analgesic (fentanyl or promedol). Ataralgesia is used for anaesthesia of patients with high anaesthesiological risk (children, elderly people, etc.).

6. Treatment of traumas, burns, prevention of traumatic shock.

7. At stressful situations, for prevention of neurotic disorders in healthy people.

8. Insomnia.

9. Treatment of the withdrawal syndrome.

Because benzodiazepines are lipophilic, these drugs are easily absorbed from gastrointestinal tract and penetrate the blood-brain barrier and other tissue barriers of a body. Short-acting benzodiazepines (oxazepam, tofisopam (Grandaxin), etc.) are metabolized by way of glucuronization. Long-acting drugs undergo demethylation with formation of active metabolites. Non-metabolized drugs and their metabolites are excreted mainly through kidneys and partly – through intestine.

Side effects of benzodiazepines are drowsiness, decreased capacity to work, muscular weakness, slowdown of psychomotor reactions and mental functions, dysmenorrhea, reduced libido, etc. Benzodiazepines are contraindicated for outpatients, whose work needs increased attention and reaction. Sometimes, benzodiazepines exhibit toxicity for fetus.

Long-time intake of benzodiazepines leads to the drug dependence (psychical and physical). In this case, sudden discontinuation of a tranquilizer intake can provoke insomnia, enxiety, depression, and convulsions. An increase of sensitivity to light and sound and changes of visual perception are also typical. For prevention

of the drug dependence, it is necessary to prescribe tranquilizers by short courses (7–10 days), to avoid sudden drug discontinuation, and to decrease a taken dose bit by bit.

It should be noticed that a long-time intake of tranquilezers is accompanied by development of tolerance that leads to reduction of their efficacy.

Ethyl alcohol potentiates effects of tranquilizers and such combination may lead to coma, sharp lowering of blood pressure, respiratory inhibition, and other symptoms of acute poisoning. *Flumazenil*, antagonist of benzodiazepine receptors, is used to treat such poisoning. There is evidence about antagonism between benzodiazepine derivatives and euphilline. Symptomatic treatment is also provided. It should be noticed that hemodialysis is ineffective in case of poisoning by benzodiazepines.

Agonists of Serotonin Receptors

Buspirone is an agonist of 5-HT_{1A} receptors. Excitation of these receptors is accompanied by development of autoinhibitory effect that leads to reduction of synthesis and release of serotonin. Buspirone exhibits expressive anxiolytic effect which develops during 1–2 weeks. The drug has no sedative, muscle relaxant, and anticonvulsive effects. Taken orally buspirone is readily absorbed from gastrointestinal tract, biotransformated in the liver, and excreted by kidneys. The drug is well tolerated by patients. Its side effects are headache, dispepsy, and irritability.

Tranquilizers with Different Mechanisms of Action

Amizylum (Benactyzine) blocks central M-cholinergic receptors in the reticular formation of the brain. The drug exhibits anxiolytic, sedative, anticonvulsive, antitussive, anaesthetic, and antihistaminic effects. Blockage of peripheral M-cholinergic receptors can cause dry mouth and mydriasis. Also, amizylum reduces the spasm of smooth muscles. The drug is taken orally 3–4 times a day. Amizylum is easily absorbed from gastrointestinal tract and excreted through kidneys.

Trimetozine (Trioxazine) has weak tranquilizing effect which is combined with stimulating action. The drug improves mood and does not cause drowsiness and slowdown of psychomotor reactions. Trioxazine is well tolerated by patients.

Daytime Tranquilizers

Daytime tranquilizers are represented by pharmacological agents of the different pharmacological groups: agonists of benzodiazepine receptors (*hydazepam, tofisopam (Grandaxin), clorazepate dipotassium (Tranxene),* and *mezapam),* α-adrenoblocking drug *pyrroxane,* nootropic drug *nootropil,* and $GABA_B$-receptor agonist *phenibut.*

Besides anxiolytic, daytime tranquilizers can exhibit sedative, muscle relaxant, and anticonvulsive effects. But sedative and muscle relaxant effects of these drugs are significantly reduced. Sometimes, the sedative effect of drugs is accompanied by some stimulating action. Due to this, daily tranquilizers cause insignificant reduction of working capacity. These drugs are preferable to treat children, elderly patients, and weakened patients.

Tranquilizing activity is also typical for β-adrenergic antagonists which easily penetrate the blood-brain barrier (e. g., *propranolol*).

Sedative Drugs

Sedative agents are drugs which decrease the excitability of the central nervous system. These drugs concede to neuroleptics and tranquilizers in a degree of inhibitory action upon the CNS. Unlike tranquilizers, sedative drugs don't eliminate negative emotions (like anxiety, fear, etc.). Sedative agents are ineffective in psychical disorders.

Sedative drugs are classified as follows:

1. Bromides: *sodium bromide* and *potassium bromide.*

2. Sedative drugs of the plant origin: *tinctures infusions of Valeriana, motherwort (Leonurus), Passiflora, peony,* etc.

3. Combined drugs: *corvalole, barbamil, cardiovalen, Novopassit, Persen,* etc.

4. Barbiturates in subhypnotic doses (1/3–1/10 hypnotic doses): *phenobarbital.*

The mechanism of action of sedative drugs is not sufficiently studied. It is known, that sedative agents do not influence certain cellular receptors and neurotransmitters. The base of sedative action is their influence upon cortex due to increase of inhibitory processes without affecting excitation processes. Thus, sedative drugs restore the balance in nervous processes.

Sedative drugs exhibit the following pharmacological effects:

1. Sedative effect without significant changes of normal functions of the central nervous system. Drugs decrease excessive irritability.

2. Sedative agents increase the effect of hypnotics and analgesics.

3. Sedative drugs facilitate the onset of sleep and increase the depth of sleep. But these drugs have no own hypnotic effect.

4. Bromides exert antiepileptic properties, but significantly concede to other antiepileptic agents.

There are the following indications for the use of sedative drugs:

1. Increased irritability, nervousness, and neurosis.

2. Dystonia of inner smooth muscle organs and discomfort in the heart.

3. Insomnia.

4. Initial forms of hypertensive disease.

5. Epilepsy (for bromides).

Bromides are easily absorbed in gastrointestinal tract. Drugs are excreted mainly through the kidneys. Because the speed of their elimination is rather low (1–2 months), bromides tend to accumulate in the body. Thus, long-time administration of bromides can result in chronic poisoning – bromism. The main symptoms of bromism are weakness, sleepiness, apathy, decreased memory, acneiform eruption on the skin (bromide acne); inflammation of mucous membranes of gastrointestinal tract and respiratory system accompanied by cough, rhinitis, conjunctivitis, and diarrhea. At occurrence of these sumptoms, bromides intake should be interrupted. A treatment of

bromism includes intake of high quantity of sodium chloride (20–25 grams a day), plentiful drink of water, and intake of diuretics.

Except sedative effect, drugs of Valeriana also exhibit antispasmodic action and relax the smooth muscles of inner organs. These drugs have low toxicity; therefore, a long-time intake is possible.

Table 19 – Drugs for prescription

Drug name (Latin)	Single dose and route of administration	Drug product
Diazepamum	Orally 0.005–0.015 g 3 times a day; intramuscularly or intravenously 0.01–0.02 g 1–3 times a day	Tablets 0.005 g; ampoules 2 ml of 0.5% solution
Phenazepamum	Orally 0.00025–0.001 g 1–2 times a day	Tablets 0.0005 or 0.001 g
Nitrazepamum	Orally 0.005–0.01 g 1–2 times a day	Tablets 0.005 or 0.01 g
Gidazepamum	Orally 0.02–0.05 g 3 times a day	Tablets 0.02 or 0.05 g
Lithii carbonas	Orally 0.3–0.6 g	Tablets 0.3 g
Natrii bromidum	Orally 0.5–1.0 g 3–4 times a day	Tablets 0.5 g
Tinctura Valerianae	Orally 20–30 drops 3–4 times a day	Tinctura 30 ml
Tinctura Leonuri	Orally 30–50 drops	Tinctura 25 ml

Step 1. Tasks for Self-Control
Anxiolytic Drugs (Tranquilizers) and Sedative Drugs

1. A patient has taken the mixture prescribed by the neuropathologist for neurasthenia for 2 weeks. The patient felt better but developed coryza, conjunctivitis, rash, inertia, decrease in memory. Bromism was diagnosed. What should be prescribed to decrease symptoms?

A. Diazepam.

B. Sodium chloride.
C. Asparcam.
D. 5 % glucose solution.
E. Polyglukin.

2. A patient, receiving diazepam to treat neurosis, complains of toothache. A doctor administered him an analgesic, but its dose was lower than average therapeutic dose. What phenomenon did the doctor consider while prescribing the patient an analgesic drug in a reduced dose?

A. Drug dependence.
B. Potentiation.
C. Cumulation.
D. Tolerance.
E. Summation.

3. A 42-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 250 mg/dl. Hospital records show a prior hospitalization for alcohol related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal?

A. Phenytoin.
B. Pentobarbital.
C. None.
D. Phenobarbital.
E. Diazepam.

4. A student asked a doctor to help him to overcome the fear of stomatological manipulations. What drug has the doctor advised to take?

A. Pyracetam.
B. Aminazine.
C. Droperidol.
D. Diazepam.
E. Dimedrol.

5. A woman, who leads an active lifestyle, has appealed to a polyclinic with complains of bad mood, migraine, emotional lability, heart pain. What drug for neurosis treatment should be prescribed, taking into consideration that the patient spends a lot of time at work?

A. Hydazepam.
B. Phenobarbital.
C. Aminazine.
D. Phenazepam.
E. Triftazine.

6. To perform oral surgery a dentist prescribed a combination of drugs with the purpose of analgesia. What tranquilizer – the derivative of benzodiazepine – is used for this purpose?

A. Diazepam.
B. Aminazine.
C. Droperidol.
D. Trioxazine.
E. Sulpiride.

7. A patient suffers from repeating attacks of epileptic convulsions with loss of consciousness. What group of drugs is primarily used to eliminate seizures in this case?

A. Sedative drugs.
B. Neuroleptics.
C. Miorelaxants.
D. Analeptics.
E. Tranquilizers.

8. After the psychical trauma, a patient began to complain of alarm, anxiety, and fear. What derivative of benzodiazepine may be prescribed to the patient?

A. Heparin.
B. Analginum.
C. Bisacodyl.
D. Nitrazepam.
E. Metoclopramide.

9. A 45-year-old patient suffers from neurosis characterized by irritability, sleeplessness, and motiveless anxiety. What drug would eliminate all the symptoms?

A. Ethosuximide.
B. Diazepam.
C. Pyracetam.
D. Levodopa.
E. Caffeine sodium benzoate.

Psychostimulants

The psychostimulants are drugs, which increase the psychical and physical working capacity, improve the mood, reduce the need of sleep, and decrease the feeling of tiredness, hunger, and thirst.

Psychostimulants are classified as follows:

1. Phenylalkylamine derivatives: *amphetamine (phenamine).*
2. Sidnone imines derivatives: *sydnocarb (mesocarb).*
3. Piperidine derivatives: *meridilum (methylphenidate), pyridrolum.*
4. Methylxanthines (purine derivatives): *caffeine.*

Phenylalkylamines

The first psychostimulant *phenamine (amphetamine)* was synthesized in 1910. This agent increases motor and psychical activity, reduces tiredness, improves mood, and reduces the need for sleep. But these effects develop due to the use of reserve capabilities of the body. Therefore, systematic intake of such drugs is dangerous. After intake of such drugs, the high-grade rest is necessary for restoration of energy reserves of the body.

Phenylalkylamines activate adrenergic transmission in the body (both in the central nervous system and in the inner organs) and regulate cellular metabolism.

Mechanism of action of phenylalkylamines is associated with the following:

1. Phenylalkylamines are indirect adrenomimetics. These drugs increase the release of catecholamines into synaptic cleft that leads to activation of postsynaptic receptors.
2. Phenylalkylamines slow down reuptake of mediators from the synaptic cleft that also increases action of catecholamines upon postsynaptic receptors.
3. Phenylalkylamines are reversible inhibitors of MAO.

Thus, phenylalkylamines significantly activate transmission of nervous impulses by means of noradrenaline, adrenaline, and dopamine. The degree of activation is directly proportional to the drug dose.

Pharmacological effects of phenylalkylamines are given below.

1. Psychostimulating effect. Phenylalkylamines reduce the mental tiredness, eliminate drowsiness, improve mood, cause mild euphoria and a desire to work. These drugs increase volume of temporary memory (but the transfer of information to long-term memory is not increased). Phenamine improves performance of a stereotyped work. Phenylalkylamines temporary suppress the need to sleep (to 10–12 hours). But, a long-term high-grade rest is necessary after the drug intake. Phenylalkylamines reduce the effects of hypnotics and other central nervous system depressants.

2. Phenylalkylamines exhibit typical doping effect: physical endurance and speed of work performance are increased.

3. Phenylalkylamines stimulate cardiovascular system. Tachycardia, icreased stroke volume and cardiac output, vasoconstriction, increased blood pressure, and reduced cerebral circulation are observed.

4. Phenylalkylamines increase concentration of glucose, lactate, pyruvate, and free fatty acids in the blood. These effects develop due to activation of glycogenolysis in the liver and skeletal muscles and lipolysis in the fat tissue.

5. Anorexigenic effect (reduction of appetite) is due to stable excitation of saturation centre which, in turn, inhibits hunger centre.

6. Analeptic effect (stimulation of respiratory centre).

7. Posibility of drug dependence (psychical and physical) in case of repeated drug intake. Therefore, all psychostimulants are considered as potential drugs of abuse.

Repeated phenamine intake is accompanied by its accumulation in the body.

Potentially, phenamine may be used to treat neurotic disorders, poisoning by drugs which inhibit the central nervous system, and to increase working capacity. But practically, phenamine is not used in medicine because it can cause drug dependence.

Sidnone Imines Derivatives

Sydnocarb is less toxic agent than phenamine. Psychostimulating effect of agent develops gradually and lasts long. Peripheral sympathomimetic effects of sydnocarb are reduced. This agent does not cause marked euphoria and motor excitement. For avoiding insomnia, sydnocarb should be prescribed in the first part of a day. An overdose of sydnocarb leads to excitement, insomnia, and increase of blood pressure.

Piperidine Derivatives

Meridilum (methylphenidate) and *pyridrolum* are piperidine derivatives which stimulate the central nervous system. Pyridrolum exhibits higher psychostimulating effect than meridilum does, but this effect is less than that of phenamine. Both drugs do not cause undysirable cardiovascular effects.

Methylxanthines (Purine Derivatives)

Caffeine is alkaloid contained in tea leaves, seeds of coffee, cocoa and other plants. Caffeine exhibits psychostimulating effect owing to blockage of phosphodiesterase – enzyme hydrolyzing cAMP. Inhibition of phosphodiesterase leads to accumulation of cAMP both in the cells of peripheral tissues (heart, fat tissue, smooth muscles of inner organs, skeletal muscles, etc.) and in the central nervous system. cAMP is a second messenger participating in transduction of signal from mediator.

Also, blockage of A_1 and A_2 adenosine receptors by caffeine plays an important role in its mechanism of action. It is known that adenosine inhibits the central nervous system activity.

Caffeine activates psychical activity; increases mental and physical capacity to work, and motor activity. The effects of caffeine depend on the type of nervous system and drug dose. In low doses it exerts stimulating action and in high doses – inhibitory effect. For the “weak” type of the nervous system the effect of excitement is reached

by introduction of low doses of caffeine. Patients with a “strong” type of nervous system require higher doses of caffeine.

The following pharmacological effects are typical for caffeine:

1. Psychostimulating effect is the result of activation of psychical activity, physical and mental capacity to work, and temporary reduction of fatigue and drowsiness.

2. Analeptic effect (stimulation of respiration and blood circulation) is the result of direct stimulating influence upon respiratory and vasomotor centres of medulla oblongata. The depth and frequency of respiration is increased. Stimulation of vasomotor centre results in peripheral vasoconstriction and elevation of blood pressure.

It is necessary to notice, that cardiovascular effects of caffeine are the result of both central and peripheral drug’s influence. Caffeine increases the tone of vagus nerve that leads to bradycardia. But direct influence of caffeine upon heart is accompanied by increase of heart rate and cardiac contraction force. Summary effect depends on the dominant component (peripheral or central).

The increase of vasomotor centre tone (central component) under the influence of caffeine is accompanied by the spasm of peripheral vessels and by the increase of blood pressure. Direct influence of caffeine upon the vessels results in decrease of vessels tone (especially vessels of skeletal muscles, of heart, and of kidneys). Summary effect depends on the dominant component. In case of marked hypotension, caffeine administration results in increase of blood pressure. In healthy persons, caffeine does not decrease blood pressure despite of its predominant direct influence upon the vessels. It is due to increased heart work. Caffeine initially causes relaxation of cerebral vessels replaced by increase of their tone.

3. Diuretic effect of caffeine is the result of kidneys blood flow improvement and of the decrease of sodium and water reabsorption in the nephron.

4. Caffeine increases the secretion of gastric juice owing to stimulation of parasympathetic nervous system (vagus nerve).

5. Caffeine increases spinal reflexes due to the improving of interneuronal transmission of impulses.

Caffeine is easily absorbed from gastrointestinal tract. About 90 % of absorbed dose is metabolized by oxidation and demethylation. Unchanged caffeine and its metabolites are excreted by kidneys.

There are the following indications for the use of caffeine:

1. In healthy people, for temporary reduction of need in sleep and for increase of mental and physical work capacity.

2. Hypotension.

3. Poisoning by ethyl alcohol, opioid analgesics, and hypnotics.

4. Migraine. Caffeine is prescribed in combination with non-opioid analgesics (e. g., tablets *"Citramone"*) or alkaloids of uterine horns (e. g., tablets *"Coffetamine"*).

5. Diagnostics of secretory activity of stomach.

Arterial hypertension, atherosclerosis, glaucoma, and insomnia are contraindications to caffeine intake. Long-time caffeine intake leads to development of moderate tolerance and psychical dependence (theism).

Nootropic Drugs (Cognitive Enhancers)

Nootropic drugs are agents which stimulate a high integrative activity of brain, improve cognitive functions, memory, and capacity to learning. Unlike other psychotropic agents, nootropic drugs have no psychostimulating or psychosedative effects, do not increase physical work activity, and do not affect emotions. The nootropic effect of drugs is developed only in case of the long-time drug use (2–5 months).

Cognitive enhancers are classified as follows.

1. Pyrolidone derivatives: *piracetam (nootropil)* and *etiracetam.*

2. GABA derivatives: *aminalon (Gammalon), picamilon, pantogam,* and *phenibut (Noofen).*

3. Neuropeptides and their analogues: *Synacthen depot®, thyroliberin,* and *melatonin.*

4. Cerebrovascular drugs: *nicergoline (Sermion), vinpocetine (Cavinton), vincamine (Devincan), cinnarizine (Stugeron), pentoxifylline (Trental),* and *xanthinol nicotinate (Complamin).*

5. Pyridoxine derivatives: *pyriditol (pyritinol, Encefabol).*

6. Antioxidants: *nicotinic acid, tocopherol, emoxypine (Mexidol),* and *thioctic acid (Berlithion).*

7. Different drugs: *Cerebrolysin, Actovegin, Solcoseryl, potassium orotate, Tanakan, Memoplant, glycine,* and *glutamic acid.*

Mechanism of action of nootropic drugs is mainly associated with changes of bioenergetic processes in neurons. Nootropic drugs increase synthesis of ATP, proteins, and RNA in neuronal cells; improve glucose utilization; increase activity of adenylyl cyclase, phospholipase A_2, phosphokinase A_1 and A_2; stimulate metabolism of phosphatidyl choline and phosphatidyl ethanolamine; and reduce cortical release of proline. Also, nootropic drugs stimulate reparation of neuronal membranes, increase GABAergic, adrenergic, dopaminergic, and glutamatergic transmission, and increase concentration of acetylcholine and serotonin in the central nervous system.

Nootropic drugs improve memory, verbal functions, and mental activity; facilitate training; increase brain tolerance to hypoxia and influence of different toxins; decrease vertigo, headache, drowsiness, and apathy. It should be noticed that these drugs do not influence higher nervous activity of healthy persons.

Cognitive enchancers are widely used to treat pathological states which are caused or accompanied by disorders of cerebral circulation and metabolism in the central nervous system: insults, mental retardation of children, cranial traumas, epilepsy, senile dementia, atherosclerosis, hypertensive disease, alcoholism, drug dependence, neurosis, cerebral ischemia, etc.

Piracetam (nootropil) is the most commonly used agent of this group. Piracetam is a pyrolidone derivative. The drug is taken orally or administered parenterally. Its side effects are sleep disorders,

allergic reactions, and dyspepsia. Piracetam is contraindicated at pregnancy and acute renal failure.

Aminalon (Gammalon) is GABA derivative. The drug improves cerebral circulation, exhibits anticonvulsive and hypoglycemic (at hyperglycemia) effects, reduces blood pressure at arterial hypertension, slows down heart rate. Contraindication to aminalon use is individual intolerance of the drug.

Vinpocetine (Cavinton) is derivative of alkaloid of lesser periwinkle (*Vinca minor*). The drug dilates cerebral vessels, improves assimilation of glucose, blood supply, and oxygenation of brain, decreases platelets aggregation, and icreases cAMP level. Vinpocetine is contraindicated at pregnancy, lactation period, severe ischemic heart disease, and cardiac arrhythmias.

Nicergoline (Sermion) is α-adrenergic antagonist. The drug decreases vascular tone, improves cerebral circulation, activates metabolism, increases supply of oxygen and glucose to cerebral tissues, decreases blood pressure in patients with hypertensive disease.

Cinnarizine (Stugeron) is derivative of piperazine. The drug blocks calcium channels. Cinnarizine decreases spasm of cerebral vessels, platelets aggregation, and exhibits antihistaminic activity. The drug does not decrease systemic blood pressure. Cinnarizine is manufactured in combination with piracetame under the trade name *"Phezam®"*.

An antispasmodic drug *pentoxifylline (Trental)* blocks phosphodiesterase that leads to accumulation of cAMP. In turn, cAMP competes with adenosine for binding with adenosine receptors. Trental increases oxygen concentration in the cerebral tissues, improves microcirculation, decreases platelets aggregation, increases the elasticity of membranes of erythrocytes, improves blood fluidity. Trental is used to treat disorders cerebral circulation, disorders of blood supply in eye, heart, kidneys, functional hearing impairment, etc.

Sodium oxybutyrate is sodium salt of γ-aminobutyric acid (GABA). The drug exhibits some nootropic activity and marked antihypoxic effect, icreases resistance of brain, heart, and retina to

hypoxia. Also, sodium oxybutirate exhibits sedative, hypnotic, and central myorelaxating effects. High doses of the drug cause general anaesthesia. Sodium oxybutyrate potentiates effects of analgesics and other central nervous system depressants.

Phenibut (Noofen) is phenyl derivative of GABA. The drug exhibits nootropic and anxiolytic activity.

Nootropic drugs include also derivatives of some vitamins: *pantogam, picamilon,* and *pyriditol*. Pantogam is a derivative of GABA and pantothenic acid. Pyriditol consists of 2 molecules of pyridoxine connected by disulphide bond. Both drugs activate brain metabolism and exhibit antihypoxic effect. Picamilon contains residues of GABA and nicotinic acid in its molecules. The drug exhibits nootropic effect and improves cerebral circulation.

Drugs which are Used to Treat Disorders of Crebral Circulation

Disorders of cerebral circulation are one of the main causes of mortality and disability of population. This patology develops due to functional disorders and organic damages of permeability of cerebral vessels (spasm, embolism, thrombosis, atherosclerosis, hemmoragies). Disorders of cerebral circulation requires emergency pharmacological care.

Drugs which improve cerebral circulation are classified as follows:

1. Drugs influencing platelets aggregation and blood clotting.

1.1. Antiaggregants: *acetylsalicylic acid* and *ticlopidine.*

1.2. Anticoagulants: *heparin, low-molecular-wheigh heparins, syncumar, warfarin, phenylin,* etc.

2. Drugs increasing cerebral blood flow and brain resistance to hypoxia.

2.1. Blockers of L-type calcium channels: *nimodipine, cinnarizine (Stugeron),* and *flunarizine.*

2.2. Derivatives of alkaloids of lesser periwinkle: *vinpocetine.*

2.3. Derivatives of ergot alkaloids: *nicergoline (Sermion).*

2.4. Nicotinic acid derivatives: *xanthinol nicotinate (Complamin).*

2.5. Nootropic drugs: *aminalon, piracetam,* etc.

2.6. Methylxanthine derivatives: *pentoxifylline (Trental).*

2.7. Myotropic spasmolytics: *papaverine hydrochloride, Nospa (drotaverine),* and *dibazol (bendazol).*

2.8. Protein hydrolysates: *Cerebrolysin, Actovegin,* and *Solcoseryl.*

Drugs influencing platelets aggregation and blood clotting are described in the correspondent chapter.

Drugs Increasing Cerebral Blood Flow and Brain Resistance to Hypoxia

Blockers of L-type calcium channels

This group is representated by such drugs as *nimodipine, cinnarizine (Stugeron),* and *flunarizine.* These drugs block L-type calcium channels in the cellular membranes and prevent calcium entrance in the cells of smooth muscles and thrombocytes. It leads to reduction of the tone of cerebral arterioles, elimination of their spasm, and decrease of platelets aggregation. Cerebral blood flow is increased. Impaired mental function is restored. These drugs are well tolerated by patients. Their possible side effects are dispepsy, headache, drowsiness, and dry mouth.

Derivatives of alkaloids of lesser periwinkle

Vinpocetine (Cavinton) is a semisynthetic derivative of alkaloid of a periwinkle plant. The drug inhibits phosphodiesterase that results in cAMP accumulation. It leads to reduction of vascular tone, decrease of platelets aggregation, and increase of erhythrocytes elasticity. Vinpocetine normalizes blood flow and metabolism in brain tissues. The drug is taken orally or administered intravenously drop-by-drop. Cavinton is used to treat neurological and psychical disorders on the background of cerebral circulation derangement, hypertensive encephalopathy, memory impairment, vertigo, ischemia of eye tissues,

in postapoplectic period, etc. Its side effects are hypotension, tachycardia, and cardiac arrhythmias.

Derivatives of ergot alkaloids

Nicergoline (Sermion) is a derivative of ergot alkaloid and nicotinic acid. The drug blocks α-adrenergic receptors and exhibits myotropic antispasmodic action. Nicergoline dilates cerebral and peripheral vessels, improves protein synthesis, and reduces platelets aggregation. Sermion is used in the treatment for disorders of cerebral and peripheral circulation, migraine, and ischemia of an optic nerve. The drug can cause such side effects as dispepsy, hypotension, skin redness, and pruritus.

Nicotinic acid derivatives

Xanthinol nicotinate (Complamin) is a derivative of nicotinic acid and theophylline. The drug dilates peripheral vessels, improves cerebral blood flow, decreases hypoxia of the central nervous system, and inhibits platelets aggregation. Like theophylline, Complamin increases myocardial contraction. The drug is taken orally or administered intramuscularly and intravenously. Xanthinol nicotinate is used to treat obliterating endarteritis, Raynaud's disease, diabetic angiopaty, disorders of cerebral circulation, and migraine. The most commont side effect of Complamin is hypotension.

Nootropic drugs

Aminalon and *piracetam* are derivatives of GABA. Picamilon is a derivative of GABA and nicotinic acid. These drugs are low toxic agents. Nootropic drugs improve cerebral blood flow (aspecially picamilon), functional activity of neurons, and exhibit antihypoxic action. Picamilon has also anxiolytic effect which is not accompanied by sedation. These drugs eliminate spasms of cerebral vessels, increase physical and mental capacity in postapoplectic period, after psychoemotional stress and overwork.

Methylxanthine derivatives

Pentoxifylline (Trental, Agapurin) is a derivative of theobromine. The drug blocks phosphodiesterase that leads to cAMP accumulation. Pentoxifylline relaxes vessels, inhibits platelets aggregation, reduces blood viscocity, increases erhythrocytes elasticity, and improves microcirculation. Trental is used to treat disorders of cerebral circulation due to spasms or sclerosis, diabetic angiopaty, disorders of eye blood circulation, etc. Its side effects are dizzinness, dispepsy, and face redness.

Myotropic spasmolytics

Papaverine hydrochloride, No-Spa (drotaverine), and *dibazol (bendazol)* eliminate spasms of smooth muscles including cerebral vessels. These drugs are well tolerated by patients.

Protein hydrolysates

Cerebrolysin, Actovegin, and *Solcoseryl* are easily penetrate the blood-brain barrier and restore violated metabolism in ischemic regions of the brain. These drugs exhibit membranostabilizing and antioxidant properties and protect neurons from damages.

Drugs for Migraine Treatment

Migraine is widespread form of disorders of cerebral circulation caused by dysfunction of vasomotor regulatory mechanisms. Women suffer from migraine more often (75 % cases). Migraine is manifested by attacks of unilateral headache which is accompanied by nausea, vomiting, visual and auditory disordrs, paresthesia, muscular stiffness, etc. Migraine attacks repeat during many years; their duration is from 4 to 72 hours.

Serotonin plays an important role in migraine development. It stimulates 5-HT_{2A}-serotoninergic receptors which leads to spasm of arteries and veins. Activation of 5-HT_1-serotoninergic receptors is accompanied by dilation of peripheral vessels and constriction of

cerebral vessels. Serotonin dilates arterioles and constricts venules which leads to the increase of pressure in capillaries. Besides, serotonin increases permeability of capillar wall for proteins. Today, 5-HT_{1D} and 5-HT_{1B} serotoninergic receptors are considered to play the main role in migraine pathogenesis.

Drugs used in migraine treatment are classified as follows:

1. Drugs used to eliminate acute migraine attacks.

1.1. Alkaloids of ergot: *ergotamine* and *dihydroergotamine.*

1.2. Indole derivatives: *sumatriptan (Imigran).*

1.3. Non-opioid analgesics: *ibuprofen, paracetamol, acetylsalicylic acid, naproxen, indometacin,* etc.

2. Drugs used to prevent migraine attacks.

2.1. β-Adrenergic antagonists: *anaprilinum (propranolol), atenolol,* and *metoprolol.*

2.2. Tricyclic compounds: *pizotifen (Sandomigran).*

2.3. Lyserginic acid derivatives: *methysergide.*

2.4. Non-opioid analgesics: *naproxen.*

2.5. Tricyclic antidepressants: *amitriptyline.*

2.6. Antiepileptic drugs: *carbamazepine* and *clonazepam.*

Ergot alkaloids *ergotamine* and *dihydroergotamine* block α-adrenergic, serotoninergic, and dopaminergic receptors which leads to reduction of amplitude of oscillation of cerebral vessels.

Sumatriptan (Imigran) is a selective agonist of 5-HT_{1D}-receptors. Its action leads to an increase of the tone of cerebral vessels and reduction of headache. The drug is taken orally and administered subcutaneously or intranasaly. Its duration of action is about 12 hours. Side effects of sumatriptan are spasm of coronary vesssels, nausea, vomiting, vertigo, feeling of heat, etc.

Methysergide is an antagonist of 5-HT_2-serotoninergic receptors. The drug has high efficacy but its clinical use is restricted owing to its toxicity. The intake of methysergide during more than 5–6 weeks can cause renal failure and retroperitoneal fibrosis. Nausea, vomiting, and diarrhea are also possible side effects of methysergide.

Pharmacodynamics and pharmacokinetics of other drugs for migraine treatment are given in correspondent chapters.

Adaptogens

Adaptogens are drugs of natural origin which exert mild stimulating influence upon the central nervous system, endocrine glands, metabolism, and increase the body resistance to adverse environmental effects.

Adaptogens are classifies as follows:

1. Galenical preparations of plant origin: *tinctures and extracts of Ginseng, Schizandra, Aralia, Leuzea, Eleutherococcus, Rhodiola; Saparalum* (complex of ammonium salts of glycosides of Aralia mandshurica roots).

2. Drugs of animal origin: *pantocrin* (liquid alcoholic extract from antlers of maral) and aquabiotic preparations.

Adaptogens stimulate synthesis of RNA and proteins, increase activity of different enzymes, and improve reparative processes. Owing to this, adaptation of an organism to undesirable influence of external environment is increased.

Adaptogens weaken biochemical (catabolism of proteins, lipids, and carbohydrates) and functional changes at stress. These drugs increase glucose entrance in the cells and improve mobilization and oxidation of lipids. Adaptogens prevent stress-induced exhaustion of pituitary-adrenal system. Adaptogens cause “economization” of metabolism.

The following pharmacological effects are typical for adaptogens:

1. Mild stimulating action which is manifested by the increase of physical and mental work capacity, decrease of fatigue, and reduction of asthenia symptoms.

2. Increase of the body resistance to the action of damage factors: high temperature, cooling, intoxication, radiation, etc.

3. Stimulation of immunity.

4. Improvement of the blood flow, respiration, vision, and hearing.

5. Cardioprotective action.

6. Hepatoprotective action.

Adaptogens are used to treat asthenia, overstrain, radiation influence, and weakening of organism functions. These agents are widely used after infective and somatic diseases.

Side effects of adaptogens are excessive excitation of nervous and cardiovascular systems, arterial hypertension, and hyperglycemia.

Adaptogens are contraindicated at arterial hypertension, hemorrhages, menstruation, hemorrhagic diathesis, and increased irritability.

Actoprotectors

Actoprotectors are drugs which increase the resistance of organism to hypoxia and high temperature. Actoprotectors also increase working capacity.

Actoprotectors are classified as follows:

1. *Bemethyl.*
2. Vitamins: *tocopherol, ascorbic acid, nicotinic acid,* etc.
3. Biogenic stimulants: *aloe*, etc.

Bemethyl exhibits psychostimulating and antihypoxic effects, increases body resistance to physical exercise compounds, reduced exhaustion of mediators and oxygen demand. The drug also stimulates immunity. Bemethyl is used to treat neurosis and asthenia. The drug is prescribed after traumas, in increased physical and psychical exercise. Its side effects are nausea, vomiting, headache, discomfort in the stomach, and congestion.

Table 20 – Drugs for prescription

Drug name (Latin)	**Single dose and route of administration**	**Drug product**
1	2	3
Sydnocarbum	Orally 0.005–0.025 g 1–2 times a day (in the first part of the day)	Tablets 0.005, 0.01 or 0.025 g
Coffeinum-natrii benzoas	Orally 0.1–0.2 g 1–2 times a day; subcutaneously 0.1–0.2 g 1–2 times per day	Tablets 0.1 or 0.2 g; ampoules 1 or 2 ml of 10 % or 20 % solution

Continuation of the table 20

1	2	3
Pyracetamum	Orally, intramuscularly or intravenously 0.4–1.2 g 3 times a day	Tablets 0.2 g; capsules 0.4 g; ampoules 5 ml of 20 % solution
Bemegridum	Intravenously slowly 0.01–0.05 g	Ampoules 10 ml of 0.5 % solution
Cordiaminum	Subcutaneously, intramuscularly or intravenously 1 ml	Ampoules 1 ml
Camphora	Subcutaneously 0.2–1 g	Ampoules 1 or 2 ml of 20 % oil solution
Aethimizolum	Intravenously or intramuscularly 0.03–0.06 g 1–2 times a day	Ampoules 3 or 5 ml of 1 % or 1.5 % solution
Sulfocampho-cainum	Subcutaneously, intramuscularly or intravenously 0.2 g 2–3 times a day	Ampoules 2 ml of 10 % solution

Step 1. Tasks for Self-Control Psychostimulants, Nootropic Drugs (Cognitive Enhancers) and Analeptics

1. Analeptical remedy of reflective type from the N-cholinomimetics group was given to the patient for restoration of breathing after poisoning with carbon monoxide. What medicine was prescribed to the patient?

A. Atropine sulfate.

B. Mesatonum.

C. Adrenaline hydrochloride.

D. Pentamine.

E. Lobeline hydrochloride.

2. An aged patient complains of headache, dizziness, quick tiredness, memory impairment. Anamnesis: craniocerebral injury. Medicine of what group should be prescribed?

A. Neuroleptics.

B. Sedatives.

C. Analgesics.

D. Nootropics.

E. Hypnotics.

3. The CNS stimulation produced by methylxanthines, such as caffeine, is most likely due to the antagonism of one of the following receptors:

A. GABA receptors.

B. Adenosine receptors.

C. Cholinergic muscarinic receptors.

D. Glycine receptors.

E. Glutamate receptors.

4. A patient with respiratory depression has been delivered to a hospital. What is the pharmacological group of drugs that can stimulate breathing?

A. Analgesics.

B. Tranquilizers.

C. Neuroleptics.

D. Antidepressants.

E. Analeptics.

5. Parents have appealed to a neurologist with complaints of the disorder of mental work, reduction of learning abilities of their 9-year-old child. Mental decline, memory impairment, and low intellectual work capacity were detected. The prescription of what group of psychotropic drugs is needed in this case?

A. Adaptogenes.

B. Antidepressants.

C. Nootropic agents.

D. Tranquilizers.

E. Neuroleptics.

6. An elderly man complains of headache, dizziness, rapid fatigability, memory impairment. In the anamnesis there is a craniocerebral trauma. What group of drugs is needed to be prescribed?

A. Tranquilizers.

B. Soporific.

C. Neuroleptics.

D. Analgesics.

E. Nootropic agents.

7. It is necessary to prescribe a drug, which improves memory and mental work in case of organic damages of the brain, to a patient. What drug should be prescribed?

A. Pyracetam.

B. Caffeine sodium benzoate.

C. Nitrazepam.

D. Mezapam.

E. Diazepam.

8. A newborn child has asphyxia. What drug is it necessary to prescribe for the stimulation of breathing in the newborn?

A. Proserinum.

B. Lobeline hydrochloride.

C. Prazosin.

D. Atropine sulfate.

E. Aethymizole.

9. During a tooth extraction a patient lost consciousness. What drug is it necessary to prescribe to bring the patient out of this condition quickly?

A. Papaverine hydrochloride.

B. Amitriptyline.

C. Analginum.

D. Novocaine.

E. Caffeine sodium benzoate.

10. A 36-year-old male patient has a cardiocerebral trauma accompanied by weak breathing and thready pulse, reflexes are absent. What is the most expedient way of pyracetam introduction in this case?

A. Inhalation.

B. Rectal.

C. Subcutaneous.

D. Intravenous.

E. Peroral.

11. A patient with complaints of memory impairment and intellectual work capacity decrease after a head trauma is hospitalized into the neurology department. What medicine can be recommended to improve brain tissues metabolism?

A. Analginum.

B. Pyracetam.

C. Meridilum.

D. Sydnocarb.

E. Caffeine sodium benzoate.

Step 1. Correct Answers to Tasks for Self-Control

General Pharmacology

1. C.
2. B.
3. A.
4. E.
5. D.
6. C.
7. E.
8. A.
9. E.
10. C.
11. D.
12. B.
13. A.
14. B.
15. E.
16. E.
17. C.
18. B.
19. A.
20. B.
21. E.
22. C.
23. A.
24. E.
25. C.
26. B.
27. E.
28. D.
29. A.
30. C.
31. E.
32. C.
33. A.
34. D.
35. B.
36. E.
37. C.
38. E.
39. B.
40. A.
41. E.
42. B.
43. D.
44. E.
45. B.
46. C.
47. A.
48. E.
49. B.
50. A.
51. E.
52. E.

Drugs Affecting the Afferent Innervation

1. E.
2. C.
3. A.
4. D.
5. C.
6. E.
7. B.
8. E.
9. B.
10. D.
11. B.
12. E.
13. C.
14. B.
15. D.
16. E.
17. B.
18. A.
19. E.

Cholinomimetic Drugs

1. D.
2. B.
3. E.
4. C.
5. E.
6. E.
7. C.
8. D.
9. A.
10. E.
11. C.
12. A.
13. E.
14. D.
15. B.
16. B.
17. E.
18. E.
19. B.
20. A.
31. C.
32. D.
33. A.
34. B.
35. E.
36. A.
37. E.

M-Cholinoblocking Drugs

1. E.
2. B.
3. C.
4. C.
5. B.
6. E.
7. B.
8. A.
9. B.
10. A.
11. B.
12. D.
13. E.
14. C.
15. B.
16. E.
17. A.
18. C.
19. E.
20. B.
21. E.
22. E.
23. C.
24. B.
25. D.
26. A.
27. E.
28. B.

N-Cholinoblocking Drugs

1. D.
2. E.
3. C.
4. A.
5. E.
6. C.
7. E.
8. D.
9. B.
10. B.
11. E.
12. B.
13. D.
14. B.
15. A.
16. C.
17. B.
18. E.
19. D.
20. B.
21. E.
22. A.
23. E.
24. C.
25. B.

Adrenomimetic Drugs and Sympathomimetics

1. A.
2. C.
3. D.
4. E.
5. B.
6. D.
7. A.
8. C.
9. E.
10. C.
11. B.
12. C.
13. B.
14. E.
15. C.
16. B.
17. E.
18. D.
19. B.
20. E.
21. E.
22. B.
23. D.
24. D.
25. B.
26. A.
27. E.
28. B.
29. A.
30. D.
31. B.
32. E.
33. C.
34. B.
35. B.
36. E.
37. C.
38. E.
39. C.
40. B.
41. E.
42. A.
43. A.
44. D.
45. D.
46. C.

Antiadrenergic Drugs

1. E.
2. C.
3. B.
4. A.
5. E.
6. E.
7. C.
8. D.
9. C.
10. C.
11. E.
12. E.
13. D.
14. B.
15. A.
16. E.
17. E.
18. B.
19. C.
20. A.
21. E.
22. A.
23. D.
24. D.
25. C.
26. A.
27. E.
28. C.

General Anaesthetics

1. B.
2. C.
3. A.
4. C.
5. D.
6. E.
7. B.
8. C.
9. E.

Hypnotic Drugs. Ethyl Alcohol

1. A.
2. B.
3. B.
4. E.
5. C.
6. E.
7. D.
8. B.
9. C.

Opioid Analgesics

1. C.
2. E.
3. B.
4. B.
5. D.
6. A.
7. B.
8. D.
9. B.
10. D.
11. A.
12. B.
13. E.
14. E.
15. E.
16. B.
17. B.
18. E.
19. B.
20. A.
21. E.
22. D.
23. D.
24. B.
25. D.
26. B.
27. C.
28. B.
29. E.
30. C.

Non-opioid Analgesics

1. D.
2. E.
3. C.
4. C.
5. B.
6. E.
7. E.
8. A.
9. A.
10. E.
11. D.
12. A.
13. E.

Anticonvulsants

1. B.
2. D.
3. B.
4. D.
5. E.
6. A.
7. B.
8. E.
9. D.
10. B.
11. B.
12. E.
13. E.
14. C.
15. E.
16. A.
17. D.
18. D.
19. A.

Antipsychotic Drugs, Antidepressants, and Drugs for Mania Treatment

1. C.
2. C.
3. A.
4. E.
5. E.
6. D.
7. C.
8. D.
9. C.
10. B.
11. E.
12. E.
13. B.
14. C.
15. B.
16. B.
17. E.

Anxiolytics (Tranquilizers) and Sedative Drugs

1. B.
2. B.
3. E.
4. D.
5. A.
6. A.
7. E.
8. D.
9. B.

Psychostimulants, Nootropic Drugs (Cognitive Enchancers) and Analeptics

1. E.
2. D.
3. B.
4. E.
5.C.
6. E.
7. A.
8. E.
9. E.
10. D.
11.B.

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ФАРМАКОЛОГІЯ

Підручник
Друге видання

У двох частинах

Частина 1

(Англійською мовою)

Відповідальний за випуск І. Ю. Висоцький
Редактор С. В. Чечоткіна
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Матеріал підручника поданий відповідно до навчальної програми з фармакології та лікарської рецептури. На сучасному рівні описані питання загальної та спеціальної фармакології. У підручнику описані механізми дії, фармакокінетика, фармакодинаміка, показання та протипоказання до клінічного застосування, побічна дія основних груп лікарських засобів. Основна увага приділяється даним, які мають фундаментальне значення для підготовки майбутніх лікарів. Друге видання суттєво перероблене та доповнене схемами та інформацією про нові препарати.

Для студентів вищих медичних навчальних закладів IV рівня акредитації.