

Ministry of health of the Republic of Belarus
Educational institution
«Gomel State Medical University»

Department of general and clinical pharmacology

Authors:

O.S.Pershenkova, assistant of department

A.V.Sennikava, senior lecturer

E.I. Mikhailova, head of department, DMS, prof.

METHODOLOGICAL RECOMMENDATIONS

for a practical lesson on the discipline "Pharmacology"
for the third-year students of the Faculty of Foreign Students,
studying at the specialty 1-79 01 01 "General medicine"

**TOPIC 11: « DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM.
DRUGS FOR GENERAL ANESTHESIA. ETHANOL. HYPNOTICS »**

Time: 3 hours

Approved at the meeting of the department of general and clinical pharmacology
the protocol № 18 of 30.06.2022

LEARNING AND EDUCATIONAL GOALS, OBJECTIVES, MOTIVATION FOR LEARNING THE TOPIC

Drugs for anesthesia can cause a state of surgical anesthesia which is characterized by the switching off of consciousness, analgesia, suppression of reflex reactions and myoplegia. The main manifestations of the action of drugs for anesthesia are due to the inhibition of interneuronal transmission in the central nervous system. Synapses of different structures of the CNS have unequal sensitivity to drugs for anesthesia, which leads to the development in their action of individual stages, which are characterized by unequal severity in different drugs. General anesthesia is widely used as a method of protecting the body from aggression (superstrong stimuli) both for surgical operations in various fields of medicine and for various diagnostic procedures and treatment of certain diseases, for example, tetanus, myocardial infarction, eclampsia. This fact necessitates the knowledge of this group of medicines by physicians of various specialties.

According to modern statistical data, sleep disorders occur in more than a third of the world's population. The fight against insomnia is the paramount task of every doctor, feasible only if you have a comprehensive knowledge of the medicines of this group. Hypnotics suppress synaptic transmission in the central nervous system, facilitate falling asleep and provide sufficient duration of sleep. However, this group of drugs also has a lot of serious side effects like development of addiction and drug dependence. Mastering knowledge of the pharmacology of hypnotics will help the doctor not only to correct insomnia, but also to minimize the negative consequences of such therapy.

In medical practice, ethanol can be used not only as an external antiseptic (for surgeon hygienic handrub, cleaning the operating field, disinfection of surgical instruments, etc.), but also as a local irritant (for rubbing, compresses). In addition, ethyl alcohol is used in the manufacture of dosage forms for external use, tinctures, extracts, as solvents in chemical practice. So the physician should know ethanol's pharmacological and toxicological characteristics with the purpose of timely and qualitative assistance in alcohol poisoning and holding on lecture work among the population about the dangers of alcohol abuse.

Learning objective:

- formation of scientific knowledge about the main pharmacological effects, providing therapeutic and preventive effect of drugs on the topic of the class, indications and contraindications for their use, the interaction of drugs, their combined use for use in medical and preventive activities.

Educational purpose:

- to develop their value-personal, spiritual potential, to form the qualities of a patriot and citizen, ready for active participation in the economic, industrial, socio-cultural and public life of the country; to realize the social significance of their future professional activities, to learn to follow academic and work discipline, standards of medical ethics and deontology.

Tasks:

As a result of the study lesson, the student should

know:

- classification and basic characteristics of the studied drugs, pharmacodynamics and pharmacokinetics, indications and contraindications for their use, side effects;

- features of pharmacokinetics and pharmacodynamics, advantages and disadvantages of different dosage forms of these drugs;
- principles of research and testing of new drugs; information and reference and search systems;

be able to:

- analyze the effect of the studied drugs on the set of their pharmacological properties and the possibility of their use in medical practice; to write them in prescriptions;
- use different dosage forms of these drugs, based on the peculiarities of their pharmacodynamics and pharmacokinetics;
- work with scientific literature, search for information about the use and action of the studied drugs;

possess:

- skills in choice of drugs on the topic of the lesson;
- the rules of prescribing the studied drugs in the treatment of various diseases and pathological conditions, taking into account the indications;
- skills of dosage regime correction in case of pathological changes in functions of organs or systems responsible for biotransformation and elimination of drugs or in case of joint use of different drugs;
- skills to search, analyze and summarize information about the use and effects of the studied drugs.

Motivation for learning the topic:

- the specifics of training doctors in this specialty determines the need for students to purposefully study the main pharmacological effects, providing therapeutic and preventive effects of drugs on the topic of the class, indications and contraindications for their use, the interaction of drugs, their combined use, which will successfully complete the specialized disciplines of the specialty.

MATERIAL EQUIPMENT

Reference and informational literature, charts, tables, presentations, drug collections.

CONTROL QUESTIONS FROM RELATED DISCIPLINES

1. Physiological mechanisms of inhibition and excitation processes in the central nervous system;
2. Anatomical and functional connections of the cerebral cortex and subcortical structures;
3. Biochemical aspects of ethanol metabolism.

CONTROL QUESTIONS ON THE TOPIC OF THE CLASS

1. Definition of anesthesia. Inhalation and non-inhalation anesthesia. Anesthesia stages. Determinants of the depth of anesthesia, the rate of development and recovery from anesthesia. Requirements for an ideal drug for general anesthesia (DGA). The concept of the activity of inhaled DGA (minimum alveolar concentration). Molecular and neurophysiological mechanisms of DGA action.

2. Inhaled DGA: halothane, isoflurane, sevoflurane, dinitrogen oxide (nitrous oxide). Pharmacological characteristics.

3. Non-inhalation DGA: sodium thiopental, propofol, ketamine. Pharmaceutical characteristics.

4. Clinical application of DGA, types of anesthesia, the concept of the breadth of narcotic action. Side effects of drugs for anesthesia. Differences of means for inhalation and non-inhalation anesthesia.

5. Ethyl alcohol. Local and resorptive effect of ethyl alcohol, use in medicine. Acute poisoning with ethyl alcohol, medical help. Chronic poisoning with ethyl alcohol (alcoholism). Principles and means of treatment of alcoholism: disulfiram, apo-morphine.

6. Hypnogenic (hypnotic) drugs: triazolam, nitrazepam, zaleplon, zopiclone, zolpidem, chloral hydrate. Classification. Neurophysiological and molecular mechanisms of action of hypnogenic drugs, pharmacological effects, pharmacokinetics, side effects and toxic effects.

7. Areas of application of hypnogenic drugs, limitations of their use. Acute benzodiazepine poisoning, principles of pharmacotherapy, benzodiazepine antagonist (flumazenil). Hypnotic effect of central H1-histamine receptor blockers (diphenhydramine, promethazine). Means of correction of circadian rhythm disorders (melatonin).

PROCESS OF THE STUDY

Theoretical part

Theoretical questions are described in the appendix to the methodological recommendations.

Practical part

1. Take notes on theoretical material demonstrated by the teacher.
2. Master the methods of solving the tasks and writing out prescriptions on the topic of the class.

Theme learning control

Conducted in the form of independent written work (solution of practical problems and prescriptions for individual task).

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF STUDENTS' INDEPENDENT WORK (SIW)

The time given for independent work can be used by students for:

- preparing for the practical classes;
- completing the tasks on the topic of the class in the workbook;
- preparing thematic reports, essays and presentations;
- taking notes from academic literature.

The main methods of organizing independent work:

- completing tests and practical tasks of the electronic educational-methodical complex (EEMC) for self-monitoring and self-assessment.

The list of tasks of the SIW:

- solving practical problems in the EEMC;

- completing the test tasks of the EEMC.

Control of the SIW is carried out in the form of:

- assessment of an oral answer to a question, report, report, or solution of a task in a practical class;
- individual conversation.

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF CONTROLLED INDEPENDENT WORK OF STUDENTS (CIWS)

Recommended forms of CIWS organization:

- doing exercises on the topic of the class in the workbook;
- writing an essay on a given topic;
- preparing a report and a multimedia presentation on a given topic.

The list of tasks of the CIWS:

Topics of essays / multimedia presentations:

1. Sleeping pills: sound sleep and unpleasant consequences.
2. The social significance of alcoholism and the basics of its pharmacotherapy.

Forms of control of CIWS realization:

- checking and grading an essay on a given topic;
- checking and grading a multimedia presentation on a given topic.

LIST OF REFERENCES

1. Kharkevitch, D.A. Pharmacology: textbook for med. students: transl. of 12th ed. of Russ. textbook "Pharmacology" (2017) / D.A. Kharkevitch. - 2nd ed. - Москва: ГЭОТАР-Медиа, 2019. - 676 с.: ил., табл. - Рек. ФГАУ "ФИРО". – Режим доступа: <http://www.studmedlib.ru/book/ISBN5970402648.html> – Дата доступа: 23.05.2022.
2. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего мед. образования: в 2 ч.=Drugs in short: partical workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 1. – Гомель: ГомГМУ, 2020. – 56с. – Режим доступа: <http://elib.gsmu.by/xmlui/handle/GomSMU/7128> – Дата доступа: 23.05.2022.
3. Кратко о лекарственных средствах: учебно – методическое пособие для студентов 3 и 6 курсов факультета иностранных студентов, учреждений высшего мед. образования: в 2 ч.=Drugs in short: partical workbook for 3 and 6 year students Faculty for International Students of medical higher educational institutions: in 2 parts / Е.И. Михайлова [и др.]. – Ч. 2. – Гомель: ГомГМУ, 2020. – 76с. – Режим доступа: <http://elib.gsmu.by/xmlui/handle/GomSMU/7129> – Дата доступа: 23.05.2022.
4. Rang and Dale's Pharmacology / J.M. Ritter [et al.]. - 9th ed. - Edinburg [et al.]: Elsevier, 2020. - xvi, 789 p.: ill., tab. + Student consult online.

General anesthesia (narcosis) – a state of temporary induced loss of sensation or awareness [1-15].

Components of general anesthesia:

- sleep
- unconsciousness and amnesia
- analgesia
- paralysis (muscle relaxation)
- reflex loss

Guedel's classification of anesthesia stages

Stage	Characteristics
I – stage of analgesia or disorientation (3-5 min)	From beginning of induction of general anesthesia to loss of consciousness. ↓ pain sensitivity, disruption of orientation
II – stage of excitement or delirium (up to 20 min)	From loss of consciousness to onset of automatic breathing. Eyelash reflex disappear but other reflexes remain intact and coughing, vomiting and struggling may occur; respiration can be irregular with breath-holding.
III – stage of surgical anesthesia <i>Plane I –</i> <i>Plane II –</i> <i>Plane III –</i> <i>Plane IV –</i>	From onset of automatic respiration to respiratory paralysis. From onset of automatic respiration to cessation of eyeball movements. Eyelid reflex is lost, swallowing reflex disappears, marked eyeball movement may occur but conjunctival reflex is lost at the bottom of the plane From cessation of eyeball movements to beginning of paralysis of intercostal muscles. Laryngeal reflex is lost although inflammation of the upper respiratory tract increases reflex irritability, corneal reflex disappears, secretion of tears increases (a useful sign of light anesthesia), respiration is automatic and regular, movement and deep breathing as a response to skin stimulation disappears. From beginning to completion of intercostal muscle paralysis. Diaphragmatic respiration persists but there is progressive intercostal paralysis, pupils dilated and light reflex is abolished. The laryngeal reflex lost in plane II can still be initiated by painful stimuli arising from the dilatation of anus or cervix. This was the desired plane for surgery when muscle relaxants were not used. From complete intercostal paralysis to diaphragmatic paralysis (apnea).
IV – (up to 30 min)	From stoppage of respiration till death

General anesthetics [1-15]

Classification	Drugs for inhalational anesthesia		Drugs for non-inhalational anesthesia		
	<i>Liquid volatile anesthetics</i>	<i>Gases</i>	<i>Short-acting (up to 15 min)</i>	<i>Intermediate-acting (20-30 min)</i>	<i>Long-acting (>60 min)</i>
Drugs	<ol style="list-style-type: none"> 1. Fluorotane (halothane) 2. Enflurane 3. Sevoflurane (<i>Closest to the ideal anesthetic</i>) 4. Isoflurane 	<ol style="list-style-type: none"> 5. Nitrous oxide 	<ol style="list-style-type: none"> 6. Propanidide 7. Propofol 8. Ketamine 	<ol style="list-style-type: none"> 9. Hexenal 10. Sodium tyopental 	<ol style="list-style-type: none"> 11. Sodium oxybutirate
Mechanism of action	<p>Synaptic transmission of excitation in neurons of the central nervous system is inhibited due to inhibition of the release of mediators or changes in the frequency and (or) amplitude of nerve impulses.</p> <ul style="list-style-type: none"> • General anesthetics stimulate inhibition through the inhibitory ion channels: 1) chloride GABA-receptor, 2) chloride channels of the glycine receptor. • General anesthetics inhibit excitation processes by blockage the excitatory CNS receptors (NMDA receptors, cholinergic (muscarinic and nicotinic) and serotonin receptors). 				
Pharmacological effects	<ol style="list-style-type: none"> 1. Anesthesia 2. Analgesia 3. Miorelaxation 4. Potentiation of the effect of antidepolarizing muscle relaxants 5. Bronchodilation (1,4) 	<ol style="list-style-type: none"> 1. Analgesia 	<ol style="list-style-type: none"> 1. Anesthesia (6, 7) 2. Analgesia 3. Miorelaxation (6,7) 4. Bronchodilation (8) 	<ol style="list-style-type: none"> 1. Anesthesia 	<ol style="list-style-type: none"> 1. Anesthesia 2. Sedative, hypnotic 3. Antihypoxic 4. Analgesia
Indications for use	<ol style="list-style-type: none"> 1. Surgery 	<ol style="list-style-type: none"> 1. Surgery 2. Myocardial infarction 	<ol style="list-style-type: none"> 1. Induction of anaesthesia 2. Short-term operations in out-patient practice 3. Combined anesthesia 	<ol style="list-style-type: none"> 1. Induction of anaesthesia 2. Basis narcosis (short-term operations) 	<ol style="list-style-type: none"> 1. Induction of anaesthesia 2. Basis narcosis 3. Anesthesia for childbirth 4. Hypoxic cerebral edema
Side effects	<ol style="list-style-type: none"> 1. Inhibit myocardial activity and ↓ BP; 2. ↓ heart rate (HR) (1), ↑ HR (4) <p><i>! Sevoflurane does not affect cardiovascular system</i></p> <ol style="list-style-type: none"> 3. Sensitizes the myocardium to catecholamines (1,2,4) 4. ↓ tidal volume, ↑, ↓ sensitivity of the respiratory center to CO₂. 5. ↓ renal and hepatic blood flow 	<ol style="list-style-type: none"> 1. Sensitizes the myocardium to catecholamines 2. ↓ tidal volume, ↑ respiratory rate (RR) 3. ↑ respiratory rate 4. ↓ renal and hepatic blood flow 	<ol style="list-style-type: none"> 1. ↓ RR 2. ↓ HR (6,7), ↑ HR and BP (8) 3. Bronchospasm (6) 4. Thrombosis and phlebitis (6) 5. Dissociative anesthesia (8). 6. Stimulates the consumption of oxygen by the brain (8) 	<ol style="list-style-type: none"> 1. Respiratory center inhibition 2. ↑ HR and ↓ BP 3. Bronchospasm 4. ↓ intracranial pressure 	<ol style="list-style-type: none"> 1. Convulsions when rapid intravenous administration 2. In case of an overdose – respiratory depression 3. When prolonged use – hypokaemia
Contraindications	<ol style="list-style-type: none"> 1. Liver dysfunction after previous anesthesia 2. Intracranial tumors 3. Hypovolemia and severe heart disease; pheochromocytoma; catecholamines administration 	<ol style="list-style-type: none"> 1. Air embolism, pneumothorax 2. Acute ileus 	<ol style="list-style-type: none"> 1. Disturbances of cerebral circulation 2. Severe hypertension 3. Eclampsia 4. Bronchial asthma (6) 	<ol style="list-style-type: none"> 1. Respiratory failure 2. Laryngitis, tracheobronchitis 3. Bronchial asthma 	<p>Low toxicity, blood circulation and respiration are not affected!</p>

Ethanol [1-15]

Ethanol is a substance of the narcotic type of action (resorptive effect) with antiseptic action in topical application.

Use

Concentration	Use
90-95%	disinfection of surgical instruments and suture material
70%	handrub (higher concentration isn't used for this purpose since with increasing concentration, the dying properties of alcohol are enhanced)
40%	compresses (primarily as an irritant)
Vapors of ethanol	antifoaming agent for pulmonary edema

Effects on organs and systems

Organs and systems	Effect of ethyl alcohol
GIT	<i>In small concentrations</i> ethanol increases the secretion of gastric juice
	<i>In concentrations greater than 20%</i> ethanol inhibits the secretion of gastric juice, increases the secretion of mucus, reduces the activity of pepsin
	<i>In high concentrations</i> ethanol causes spasm of the pylorus and reduces gastric motility
CNS	Inhibitory effect (the stage of excitation during alcohol intoxication is associated with inhibition of inhibitory processes). After the stage of excitation with an increase in the concentration of ethanol in the blood, analgesia, drowsiness, impaired consciousness happen, spinal reflexes become oppressed.
CVS	↑ BP and tachycardia (In large doses causes collapse, possibly a disruption of contractility of the myocardium)
Thermoregulation	Increased heat dissipation due to peripheral vessels dilation because of the suppression of the vasomotor center
Urinary system	Diuretic action (inhibits the release of antidiuretic hormone)
Metabolism	Promotes accumulation of lipids in hepatocytes , causes hypoglycaemia, hyperlipidemia , reduces the amount of glycogen in the liver
Psychoemotional sphere	Long-term use of alcoholic beverages leads to the dependence and addiction.
NB!	Lethal dose – 300-400 ml of 96% alcohol taken within 1 hour or 250 ml in 30 minutes.

Severe alcohol intoxication

Symptoms :

- loss of consciousness
- acute respiratory failure (obstructive aspiration type)
- BP falls, thready pulse
- cyanotic face
- vomiting, may be involuntary urination and defecation
- hypotension of muscles
- hypothermia
- areflexion
- violation of the contractility of the heart
- possible respiratory depression.

Therapy:

- gastric lavage (when severe coma, after intubation of the trachea)
- forced diuresis
- administration of sodium bicarbonate (when acidosis)
- intravenous administration of solutions of glucose, B and C groups vitamins
- warming the patient
- in severe cases, extracorporeal detoxification (hemodialysis)

Chronic alcoholism — A disease characterized by pathological attraction to alcohol, mental and physical dependence on it. Alcoholism severely affects higher nervous activity (intellect, attention, memory, the core of the personality is destroyed). Possible development of alcoholic psychoses, peripheral polyneuritis.

Method of sensitizing therapy is based on increasing the sensitivity of the body to alcohol. For this purpose, an antabuse (teturam, disulfiram, esperal) and a substance with a teturam-like effect (for example, metronidazole) can be used. ***Teturam delays the metabolism of ethanol during the formation of acetaldehyde (inhibits the enzyme aldehyde dehydrogenase).***

This leads to the development of somatic disorders:

- Hyperemia of the face and upper body
- Increased respiration, pulse
- Nausea and vomiting
- Lower blood pressure
- Pain in the region of the heart
- Headache
- Profuse sweating

Then psychotherapeutic methods helps the patient to disgust alcohol and doctors explain a mortal danger in the use of alcohol.

Hypnotics – drugs that can cause sleep and normalize its disturbances [1-15].

Classification	Benzodiazepine derivatives	Derivatives of barbituric acid	Cyclopyrrolone derivatives and other chemical groups
Drugs	1. Nitrazepam (Eunotin, Radedorm) 2. Midazolam (Dormikum) 3. Triazolam (Chalcion)	4. Phenobarbital (Luminal) 5. Cyclobarbital (Fanodorm)	6. Zopiclone (Imovan) 7. Zolpidem (Iwadal) 8. Methaqualone (Dormutil) 9. Doxylamine (Donormyl) 10. Bromizoval (Bromural)
Mechanism of action	Stimulate specific receptors structurally-functionally associated with GABA-receptors. At the same time there is an increase in the affinity of GABA receptors for GABA and the opening of the postsynaptic membrane of GABA-ergic synapses for chloride ions. The ions of chlorine penetrate into the cells and increase the concentration of negative charges on its inner surface. This leads to hyperpolarization of the neuronal membrane, as a result of which the cells are not excited, inhibition occurs.		
Pharmacological effects	1. Sedative, 2. Hypnotic 3. Potentiating, 4. Anticonvulsant, 5. Anxiolytic (1-3), 6. Miorelaxing (1,2), 7. Amnestic (2).		1. Sedative, 2. Hypnotic, 3. Potentiating (6.8) 4. Anticonvulsant (7.8) 5. Anxiolytic (7.8), 6. Miorelaxing (6.7), 7. Amnestic (7), 8. Antihistamine (9), 9. M-cholinolytic (9).
Indications for use	1. Sleep disorders (Difficulty falling asleep, early or nocturnal awakening), including secondary sleep disturbances in mental disorders 2. Seizure syndrome (4) 3. Premedication before surgery or diagnostic procedures, introduction to general anesthesia and anesthesia maintenance, prolonged sedation in intensive care, introductory and basic general anesthesia in children (2) 3. Premedication (1, 2)		
Side effects	1. Influence on the phase structure of sleep (practically absent) 2. Ataxia (impaired coordination of movements) 3. Lethargy, muscle weakness and dizziness (sometimes) 4. Development of mental and physical dependency and withdrawal syndrome (when prolonged use)	1. Shorten the duration of the rapid eye movement sleep 2. Drowsiness, fatigue 3. Decreased efficiency, concentration of attention, lack of coordination 4. When prolonged use – psychic and physical dependence, withdrawal syndrome	1. Allergic reactions 2. Mental, behavioral disorders 3. Impaired coordination 4. Weak withdrawal syndrome, with long-term use, it is possible to develop mental and physical dependence
Contraindications	1. age under 15, 2. pregnancy, lactation, 3. severe respiratory failure, 4. hypersensitivity to drugs, 5. persons whose work is associated with a high concentration of attention (drivers)		
NB!	The difference between benzodiazepines and barbiturates: mild awakening; there is practically no effect on the phase structure of sleep; the risk of a physical dependence is low; the risk of overdose is much lower. Antidote for poisoning: flumazenil	<i>Barbiturate overdose</i> The main actions: the maintenance of breathing (artificial respiration), hemodialysis, forced diuresis, gastric lavage. <i>Death comes from respiratory arrest.</i> Gastric lavage is useless if more than 1 hour has elapsed after poisoning – barbiturates are well absorbed in the acidic medium of the stomach.	These drugs are used in patients for whom some memory impairment caused by benzodiazepines (for example, in students) is unacceptable.