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Drogovoz S.M., Kutsenko T.A., Pozdniakova A.J., Ulanova V.A.

TOXICOLOGY

SUMMARY OF LECTURES, PRACTICE AND TESTS ON TOXICOLOGY

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Authors: S.M. Drogovoz, T.A. Kutsenko, A.J. Pozdniakova, V.A. Ulanova

Reviewer: T.V. Zvyagintseva, PhD, professor, the head of Pharmacology department of Kharkiv State Medical University.

English translation reviewer: Gurko Ye.Yu., associated professor of foreign languages department of National University of Pharmacy.

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This issue is a **brief** summary of lectures, practices and tests on toxicology for students. Using this logically structured information future pharmacist will be able to solve the professional tasks.

This edition is recommended for students of universities and departments of pharmacy.

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INTRODUCTION

This issue is a **brief** summary of lectures, practice and tests on toxicology for students.

Each topic is structured in such a sequence: the title of the topic, the classification and nomenclature of medicines, their mechanism of toxic action, the interval of doses, toxicodynamics, antidotes and prevention of intoxications.

Such a structure of the information exposition teaches the students to master the topic rapidly, to find the logic connection between the drug toxic mechanism of action and toxicodynamics that helps to determine antidotes and prevention of intoxications.

Using this logically structured information a future pharmacist will be able to solve the professional tasks.

LECTURE 1
GENERAL TOXICOLOGY

Toxicology is a science about poisons *("toxicon"- poison, "logos"- science)* and their influence and interactions with the human body or other living organisms.

The appearance and development of toxicology is bound to pharmacotherapy and pharmacology. It is also connected with chemistry, botany, pharmacognosy, toxicological chemistry, hygiene.

The subject of toxicology is poison.

Poison is a substance that acts as a harmful or lethal agent to the human body.

Nowadays the problem of acute and chronic poisonings associated with application of domestic chemicals, cosmetics, medicines are very important. For example, according to the WHO data the lethality due to overdose of different medicines is about 30 % of cases per year.

It is known that any medicine depending on the dose may act as a therapeutic agent or poison.

Modern toxicology is the study about toxicity and toxic process - phenomena registrated in case of interaction of chemical agents (e.g. medicines) with living organisms.

Toxicity is a property of chemical substances (medicines) to affect the biological systems by non-mechanical way and to cause their damage and death.

So, for human body, toxicity is a disorder of the body functioning, disease or even death.

The effect of substances (medicines) that causes damage of living organisms or their components is called a toxic effect (action).

The interaction of a poison (medicine) and a biological system at the molecular level is a base of the toxic effect development. The chemical reaction or physical and chemical interaction of the biosystem (its elements) and poison are called the mechanism of the toxic action.

The toxic process (intoxication) is a reaction of the biosystem to the effect of a toxic agent (toxicant) resulting in the biosystem's damage (dysfunction), vitality suppression, and death of the organism. Parameters describing the toxic effect are the type of a toxicant, its dose, intensity of the action, intoxication development.

THE LEVELS OF INTOXICATION DEVELOPMENT:

1. The cellular level (it includes cytotoxicity: necrosis, apoptosis, mutagenicity).
2. The organ's level (includes organospecific toxicity: neuro-, hemato-, hepato-, nephrotoxicity, etc.).
3. The organism's level (includes temporary ("transit") toxic reactions, allobism, specific toxic reactions).
4. The population's level (increase of morbidity in a certain population)

Temporary toxic reaction may disappear sooner or later and include such states as irritation of the respiratory tract and eyes, sedation, sleepiness, etc.

Allobism is a stable change of the body resistance to certain factors of the environment, mental and physical overload (e.g. increase fatigue), allergy, immune suppression.

Specific toxic reaction develops in specific conditions during a certain period of life (embryotoxicity, etc.).

KINDS OF INTOXICATION:

- ✖ Depending on the duration of a toxicant and the body interaction:
- ✖ Acute (several hours or days),
- ✖ Subchronic (not more than 90 days),
- ✖ Chronic (more than 90 days)

PERIODS OF INTOXICATION:

- ✖ Contact with a toxicant;
- ✖ Latent (masked) period;
- ✖ Development of the disease (with clinical symptoms);
- ✖ Recovering or complication of the disease

Toxic effect is divided into local and systemic one. The local effect, for example, is irritation of the respiratory tract (ammonium hydroxide), affection to the eyes (miosis- cholinomimetics, morphine; mydriasis- M-cholinoblockers), inflammation and necrosis of the skin or mucous membranes (acids, alkalies).

The systemic effect is a selective damage of a certain organ or system. For example, ototoxicity (aminoglycoside antibiotics), hepatotoxicity (tetracyclines), hematoxicity (Amphotericin B).

DEPENDING ON THE POTENCY OF THE TOXIC EFFECT INTOXICATION IS DIVIDED INTO:

- ✖ Severe (dangerous for life)
- ✖ Moderate (development of complications)
- ✖ Weak intoxication

The aim of toxicology is improvement and optimization of methods providing saving of life, health and functioning of humans in case of routine and extreme contact to different chemicals.

TASKS OF TOXICOLOGY:

1. Estimation of quantitative parameters of toxicity (relationship between chemical (medicine) affection and severity of intoxication). It is toxicometry (the part of toxicology).
2. The study about mechanisms of the toxicants action, principles of the toxic process development, symptoms of intoxication (it is ***toxicodynamics***).
3. The study about ways of the toxicant coming to the body and all changes occurring from this moment till elimination (absorption, distribution, metabolism, excretion of poisons) (it is ***toxicokinetics***).

4. The study of factors influencing the toxicity of substances (properties of toxicants, peculiarities of the biological system, types of their interaction).

THE STRUCTURE OF TOXICOLOGY:

1. Experimental toxicology.
2. Preventive toxicology.
3. Clinical (medical) toxicology.
4. Industrial toxicology.
5. Ecological toxicology.
6. Toxicology of specific types of action (veterinary, military, agricultural, etc.)

Toxicants depending on the origin are biological, bacterial, the plant origin, poisons of the animal origin, inorganic substances of the non-biological origin, synthetic ones.

Medicines are found among all of them. The part of toxicology that deals with toxic effects of medicines occurring in case of their intake or application and deals with treatment and prevention of poisonings by medicines is called medical toxicology.

The properties of the toxicant determining its toxicity are the size of a molecule, physical and chemical properties, stability, chemical properties, type of the bond in the molecule, etc.

The main way of the toxic effect development is ***cytotoxicity.*** The main mechanisms of cytotoxicity are:

1. Inhibition of the energy metabolism in the cell.
2. Disorder of the intracellular Ca2+ level.
3. Inhibition of the cell proteins synthesis and cell division.
4. Damage of the cell membranes, including altering of Na+, K+, Ca 2+ flows, changes of lipid functions in the membrane permeability, the change of the electrical charge.
5. Cells with a high intensity of multiplying are highly sensitive to toxicants. These cells are embryonic, bone marrow, renal epithelium, skin, liver, GIT cells.
6. Such toxic effect is characteristic for many medicines in toxic doses such as antibiotics, antitumour, antifungal, and other medicines.

Many poisons show different intensity of intoxications depending of the ***dose.*** More often a higher dose is, the stronger intoxication occurs. This dependence between dose and effect of a toxicant is usually described by **ED50** (therapeutic effect for medicines) and **LD50** (half-lethal dose that is dose causing of death of 50 % of experimental animals). But this parameters are correct for substances with the **"dose-effect"** linear dependence.

CLASSIFICATION OF XENOBIOTICS (MEDICINES AND MEDICINAL SUBSTANCES THAT ARE UNDER STUDY) TOXICITY DEPENDING ON THE LD50 (ONE OF THE MODERN CLASSIFICATION)

Class of toxicity	Enteral route of administration (LD_{50} mg/kg)	Inhalation route (LD_{50} mg/kg)	Limit concentration mg/m^3
Highly toxic	< 15	< 1	< 1
Very toxic	15-150	1-10	10
Toxic	151-1500	11-40	100
Low toxic	>1500	>40	>100

FACTORS AFFECTING TOXICITY OF SUBSTANCES

1.Toxicokinetics
2.Toxicodynamics
3.Factors associated with the body:
- Sex
- Age
- Body weight
- Pregnancy
- Tolerance to a toxicant
- Nutrition

4.Factors associated with the toxicant:
- Dose
- Chemical structure
- Medicinal form
- Route of administration
- Intake of other substances at the same time

5.Others :
- Duration of contact to a toxicant
- Circadian rhythms
- Temperature of the environment

Antidotes are medicines that are used for treating intoxications. They are used to inactivate the poison, to prevent or eliminate the toxic effects of the poison.

Mechanisms of action of medicines used for treatment of acute intoxications

1. **Etiotropic medicines therapy. Mechanisms**
   - ✓ Chemical neutralization of a toxicant
   - ✓ Biochemical replacement of a toxicant
   - ✓ Physyological antagonism (normalization of the subcellular components structure, interaction to specific receptors)
   - ✓ Modifying of toxicants' metabolism

2. THE PATHOGENETIC MEDICINES MECHANISM

- ✓ Modulation of processes of the nerve and humoral regulation
- ✓ Elimination of hypoxia and disorders of bioenergetic processes
- ✓ Normalization of the water-salt metabolism and the acid-base equilibrium
- ✓ Normalization of permability of histo-hematic barriers
- ✓ Stopping of chemical reactions leading to the cell death

3. THE SYMPTOMATIC MEDICINES MECHANISM

- ✓ Stopping / inhibition of pain, convulsions, psychomotor excitement
- ✓ Normalization of respiration and hemodynamics

Among the listed above the most specific medicines (to the poisons) are etiotropic, then pathogenetic and, at least, symptomatic ones.

It is known that etiotropic medicines, taken in time and in a correct dose, completely stop development of intoxication.

EFFECT OCCURING AFTER APPLICATION SPECIFIC ANTIDOTES IN ACUTE INTOXICATIONS

Medicines	Expected effect	Examples
Etiotropic	Inhibition or elimination of all symptoms of intoxication	Treatment of intoxication by cyanides, use of methaemoglobin - forming substances
Pathoge-netic	Inhibition / elimination of a certain pathogenetic toxicant	Elimination of the brain hypoxia caused by respiratory irritants (chlorine) using inhalation of oxygen
Sympto-matic	Correction / elimination of the intoxication symptom	Inhibition of convulsions caused by Neostigmine using Diazepam

EXAMPLES OF ANTIDOTES USED CLINICALLY

Antidotes	Type of antagonism	Toxicants
EDTA, Unithiol, Amylnitrate	Chemical	Salts of heavy metals, cyanides
Reactivators of acetylcholineserase	Biochemical	Anticholinesterase agents
Methylene blue	Biochemical	Cyanides
Atropine Physostigmine Diazepam Flumazenil Naloxone	Physiological (it involves receptors usually)	Anticholinesterase agents Cholinoblockers GABA-blockers Benzodiazepines Narcotic analgesics (opioids)
Sodium thiosulphate Acetylcysteine Etanol	Modification of metabolism	Cyanides Paracetamol Methanol

Unfortunately, specific antidotes exist for the limited number of toxicants. Sometimes only non-specific therapy of poisonings is possible ("forced" diuresis, intake of adsorbents, washing of the GIT or skin, application of general detoxicants, etc.)

Nowadays there is the way of treatment of cardiac glycosides intoxication (for Digoxin).

It means using of immune medicines (antibodies) that are specific for Digoxin, recognizing it and form stable non-toxic chemical complexes (chemical antagonism) with Digoxin providing detoxication.

LECTURE 2:
TOXICOLOGY OF OPIOID ANALGESICS, NON-OPIOID ANALGESICS, $NSAID_S$

OPIOID ANALGESICS (OA)
Classification and medicines

Natural and semisynthetic medicines*	*Synthetic medicines*	
Morphine Codeine phosphate* Omnopone Aethylmorphine h/chl* Buprenorphine	Trimeperidine (Promedol) Sufentanyl Fentanyl Dimenoxadol h/chl Piritramide	Morphine Codeine phosphate* Omnopone Aethylmorphine h/chl* Butorphanol Pentazocine

INTERVAL OF DOSES OF OA

Drug	***Interval of the therapeutic action, mg***	***Interval of the toxic action, mg***	***Lethal doses***
Morphine	**1-20**	**60-200**	**200-400 mg**
Codeine	**2-100**	**300-800**	**800 mg**
Fentanyl	**0.05-0.1**	**0.1-2**	**2 mg**
Pentazocine	**25-100**	**350-500**	**500 mg**
Tilidine	**100-200**	**250-500**	**500 mg**
Tramadol	**100**	**400**	**0.03 mg/l**

Because of tolerance development toxic and lethal doses of OA are not estimated exactly. It is know that after 10-15 injections tolerance to OA develops and the therapeutic effect decreases 6-10 times.

TOXICODYNAMICS OF OA

- Immediatly after intake facial hyperemia, dizziness, nausea, «dreams without sleep» occur.
- After: sleepiness, pale skin, miosis, bradycardia, muscular hypertone.
- Tonic-clonic convulsions are possible; in case of severe intoxications acute respiratory failure, skin cyanosis, mucous membranes cyanosis, collapse, bradycardia, hypothermia, gastric hypertone, intestinal hypertone, urinary bladder hypertone, coma
- Thus, the main toxic effects of OA are:

- Inhibition of the respiratory centre
- Hypoxia
- Stimulation of the vagus nerve centre (bradyarrhythmia)
- Stimulation of the oculomoter nerve centre (miosis)
- Disorders of the emetic centrer tone

❑ Lethal doses of OA cause respiratory stoppage, heart stoppage and then lethal outcomes

IN CASE OF ACUTE INTOXICATION BY:

☐ **Codeine** — convulsions; complications — brain edema, pulmonary edema, pneumonia.
☐ **Buprenorphine** — inhibition of respiration.
☐ **Butorphanol** — hyperventilation, coma, acute heart failure.
☐ **Tramadol** — inhibition of respiration, convulsions, miosis, anuria, coma
☐ **Trimeperidine** — nausea, vomiting, dizziness, inhibition of respiration.
☐ **Pentazocine** — inhibition of respiration, bronchospasm, nausea, vomiting, constipation, atony of bladder, disorders of BP.
☐ **Fenthanyl** — strong inhibition of respiration.

In comparison to Morphine, Tramadol is less potent in inhibiting respiration and stimulation of the emetic centre and the centre of the oculomotor nerve.

THE MECHANISM OF THE OA TOXIC ACTION

☐ The main dangerous effect (in overdose) is inhibition of respiration and non-cardiogenic shock occurence. Respiratory insufficiency develops due to inhibition of the respiratory centre and decrease of its sensitivity to carbon dioxide because of increase of the vagus nerve centre activity and disorder of the cortical regulation of respiration. Inhibition of respiration leads to accumulation of carbon dioxide in the blood and respiratory acidosis development.
High sensitivity of the respiratory centre to OA among newborns (up to 2 months) and elderly people is explained by delayed metabolism of OA in the liver.
☐ Many OA penetrate through the placental barrier and inhibit the respiratory centre of the fetus causing asphyxia development.
☐ Stimulation of the vagus nerve and a direct spasmogenic effect to the smooth muscles tone (especially bronchi), the GIT sphincters, billiary tract, bladder.
☐ Increase of ADH (antidiuretic hormone) production and increase of the urinary tract sphincters tone result in urinary retention
☐ Increase of histamine release and stimulation of the vagus nerve centre cause the broncospasm development. Because of histamine release OA also cause the skin itching (often around the nose) and urticaria.
☐ Cardiovascular system disorders occur due to hypoxia caused by respiratory failure. The mechanism of the pulmonary edema development is connected with increase of capillary permeability in lungs caused by hypoxia. Inhibition of respiration and accumulation of carbonic acid (H_2CO_3) in the blood cause dilation of brain vessels that also increases the risk of pulmonary edema.

- Vomiting is caused by irritation of trigger-zone receptors in the medulla oblongata.
- Miosis is the result of the oculomotor nerve stimulation.
- Stimulation of the spinal cord and hypoxia of the nerve tissue caused by OA, results in convulsions, especially in children.
- After intravenous injection of OA arterial hypotension develops. It is connected with histamine release and decrease of the sympathetic nervous system tone.
- Hypothermia caused by OA is explained by their inhibitory effect on thermoregulation centre

ANTIDOTES

- Specific antidotes to OA are Naloxone and Naltrexone. They are competitive complete antogonists of opioid receptors. Naloxone should be injected i/m, i/v, 0.4 – 0.8 mg every 3-4 hours. Nal-trexone should be injected every 8-12 hours and its effect is stronger than the Naloxone's effect.
- ***Nalorphine*** is an agonist-antagonist of Morphine, eliminates hypotension, inhibits respiration, arrhythmia caused by OA

SYMPTOMATIC THERAPY

Symptom	What to do?
CNS inhibition, sleepiness, fatigue	Make a poisoned person not to sleep
Decrease of poison absorption and improvement of elimination	In the conscious state it is necessary to wash the stomach several times by 0.05%-0.1% solution of Potassium permanganate (KMg04) (it oxidizes Morphine) , also salt laxatives, activated charcoal should be given. Emetic agents are contraindicated. If it is too late to wash the stomach, a lot of drinks should be taken (strong black coffee). If the patient is unconscious sodium sulphates, castor oil + black coffee should be used rectally. Besides, sodium hydrocarbonate solution (4% solution 3-4 ml/kg) should be injected i/v. "Forced" diuresis, enterosorption, haemosorption, dialysis may be done.
Stimulation of the liver antitoxic function	Vitamines B2, B6, C, E are prescribed
Inhibition of respiration	Inhalation of the mixture of air and carbon dioxide
Pulmanary edema	Oxygenation, osmotic diuretics
Convulsions	Diazepam, muscle relaxants intubation, artificial respiration
Bradyarrhythmia, bronchospasm,	Atrophine sulphate 0.5-1 ml of 0.1% solution i/v or i/m

spasm of smooth muscles	
Hypothermia	Heating of the body
Coma	Pyracetam 20% - 50 mg/kg i/v

Administration of barbiturates, Bemegride, Magnesium sulphate, alcohol does not help!

PREVENTION OF INTOXICATIONS

- Risk factors: newborns, old people, cranio-cerebral traumas, bronchial asthma, pulmonary insufficiency, pregnancy, disorders of the liver and kidneys function, atherosclerosis, diseases of heart and lungs, mixedema, addiction to OA.
- Combined administration of OA and the CNS depressants is dangerous.
- While combining with tricyclic antidepressants OA cause disorders of the heart rate.
- MAO inhibitors increase side effects of OA: anxiety, mental disorders, inhibition of respiration.
- The combination of OA and alcohol is very dangerous!

NON-OPIOID ANALGETICS (NOA) AND NSAIDs

Classification and medicines

NOA with the central component of action	Peripheral-acting NOA (monodrugs and combined* ones)	Spasmo-analgesics
Neopharm Paracetamol Ketorolak	Sodium methamizol Pentalgin Citramon Thempalgin Sedalgin	Baralgetas Spasmalgon

Paracetamol is widespread all over the world. But it is not safe. Sometimes 2 tablets is enough to reach intoxication by Paracetamol. It is a haemato- and hepatotropic poison. It takes the second place in the USA and the first place in Greate Britain as the cause of hepatic failure.

THE INTERVAL OF DOSES FOR NOA

Medicine	The interval of the therapeutic action	The interval of the toxic action	Lethal doses
Paracetamol	< 125mg/kg	5-15 g	13-25 g
Methamizol	1-3 g	10-15 g	< 15 g
Nephopam		30-90 mg	

Paracetamol has a narrow interval of the therapeutic action, that is why intoxications are possible. Symptoms may come even in small doses depending on the general state of liver, kidneys, blood.

TOXICODYNAMICS OF PARACETAMOL

- Acute intoxication: at the very beginning – nausea, vomiting, pale skin, hyperhydrosis, abdominal pain, euphoria; in 24-36 hours – strong abdominal pain,

vomiting, dizziness, weakness, sleepiness. In 3-4 days – fever, the yellow colour of the skin, tachycardia, hypotension, urinary retention, encephalopathy, coma occur.

- Besides these symptoms, cyanosis (because of methaemoglobin formation), anemia, haemolysis, bilirubinemia, hyperactivity of liver enzymes, heart rate disorders, ICP increase, bleedings, acidosis, renal failure are possible.
- The reason of death in Paracetamol intoxication is hepatic failure, liver necrosis, brain edema
- In case of chronic Paracetamol intoxication hepatic failure always develops

IN CASE OF ACUTE INTOXICATION BY:

- ***Nephopam.*** Convulsions, sleepiness, tachycardia, hypertension, acidosis develop.
- ***Methamizol.*** Nausea, vomiting, weakness, hypothermia, convulsions, bleedings, even coma (in severe cases) occur.
- ***Ketorolak.*** Dizziness, sleepiness, euphoria, anemia, bleedings, hepato-, nephrotoxicity, hypokalemia, hyponatremia, bronchospasm occur

THE MECHANISM OF THE TOXIC ACTION OF NOA

Paracetamol

- The hepatotoxic effect is a result of Paracetamol's metabolite formation in the amount that is greater than the amount of glutathione. It leads to interaction of N-acetylbenzoquinonimine with hepatocytes and their death. Severe liver damage may be explained also by intensification of lipid peroxidation, damage of microsomal liver membranes, development of partial liver necrosis. Methaemoglobin formation is a result of methaemoglobin-reductase defficiency. It leads to haemolysis and further to inhibition of haemopoiesis.
  Metabolites of Paracetamol (paraaminophenol) accumulate in kidneys, bind to SH-groups and cause partial necrosis (the so called **"analgetic nephropathy"**). **Methamizol sodium** causes haemolysis due to formation of immune complexes that are absorbed by erythrocytes. Besides, Methamizol suppresses haemopoiesis causing agranulocytosis.
  NOA cause the ulcerogenic effect caused by inhibition of Prosaglandin E2 formation (it is responsible for protection of gastric mucous membrane).
- Neurotoxicity of NOA is associated with their ability to penetrate through the blood-brain barrier and inhibit the CNS due to inhibition of Pg E_2 formation that are responsible in the CNS for regulation of the brain blood circulation.
- The nephrotoxic effect of NOA is also associated with the blockade of Pg E2 synthesis that results in renal vasoconstriction, decrease of renal filtration and urinary retention (edema, hypertension)

ANTIDOTES FOR PARACETAMOL

- ***N-acetylcystein.*** It is a precursor of cystein and glutathione, it restores the level of glutathione and gives SH-groups for binding and detoxication of toxic Paracetamol's metabolite. Besides, it binds to non-metabolized Paracetamol and

decreases formation of its toxic metabolites; it binds to free radicals, improves tissue oxygenation and microcirculation.

- ***Methylene blue*** (tetramethylthionine chloride) is an antidote for methaemoglobin-forming substances, restores methaemoglobin

SYMPTOMATIC TREATMENT OF INTOXICATION BY NOA

Symptom / Effect	Treatment
Stopagge of absorption and stimulation of elimination	Washing of the stomach, laxatives (NOA). Intake of activated charcoal (Nephopam 50-100g)
Vomiting	Metoclopamide, Ondasetron (NOA)
Methaemoglobinemia	Methylene blue, Methionine (NOA)
Renal failure	Haemodyalysis (NOA)
Hepatic failure	Haemofiltration, haemoperfusion (NOA)
Convulsions	Diazepam (Paracetamol, Nephopam); Cloralhydrate(Methamizol)
Tachycardia	S-blockers (Paracetamol, Nephopam)

PREVENTION OF NOA INTOXICATION

- ***The group of risk:*** increased metabolism of Paracetamol or delayed rate of its detoxication; intake of rifampicin, anticonvulsants, chronic alcoholism
- Administration of Ketorolak more than 7 days is contraindicated.
- Low doses of Paracetamol in combination with alcohol may cause toxic hepatitis
- ***Nephopam, Paracetamol*** are incompatible to MAO inhibitors

NSAIDs
Classification and medicines

Derivatives of		
Salicylic acid	Phenylpropionic acid and phenylacetic* acid	Pyrazolone and indolacetic* acid
Acetylsalicylic acid (ASA) Lisine acetylsalicylate	Ketoprofen Ibuprofen Sodium diclofenac*	Phenylbutazone Indomethacine*
Oxicams and fenamates*	**Coxibs**	**Combined and other* agents**
Meloxicam Pyroxicam Niflumic acid* Mefenamic acid*	Celecoxib Roficoxib	Reopyrin Nimesulid* Sigan

Every year in the USA 70000 of cases when a person comes to hospital are registrated about 7000 of lethal outcomes connected with administration of NSAIDs.

THE INTERVAL OF DOSES OF NSAIDS

Medicine	Interval of the therapeutic action	Interval of the toxic action	Lethal doses
ASA		0.1-0.15 g/kg	5-30g (adults), 2-10 g (children)
Meloxicam	0.0075-0.015	0.015 g	Not found
Nimesulid	0.1-0.2	0.2 g	Not found
Celecoxib	0.1-0.2	0.4 g	Not found
Roficoxib	0.0125-0.025	0.05 g	Not found
Diclofenac	0.015-0.05	375 mg	Not found
Ibuprofen	0.2-0.8	> 3 g	6.8 g (children); 24 g (adults);
Indomethacin	0.005-1.0	175-1500 mg	50-150 mg/kg

TOXICODYNAMICS OF NSAIDs

The main symptoms are:

- Toxic gasroenteritis
- Nausea, vomiting, abdominal pain
- Sleepiness, headache
- Glucosuria, haematuria, proteinuria
- Toxic encephalopathy
- Pulmonary edema
- Dehydration (more often in children)
- Hypoglycemia
- Acute renal failure and hepatitis(seldom)

IN CASE OF INTOXICATION BY:

- Pyrazolone derivatives and Nabumethone - cardiotoxicity
- Ibuprofen, naproxene – acidosis, coma, convulsions
- Mefenamic acid, phenylbutazone – coma, inhibition of respiration, hypotension, convulsions.
- Ketoprofen – convulsions (seldom)
- Coxibs – thrombogenic effect
- Ibuprofen – bradycardia, hypotension

THE MECHANISM OF THE TOXIC ACTION OF NSAIDs

- ***The gastrotoxic*** (ulcerogenic) effect is bound to inhibition of COX-1 activity leading to inhibition of Pg synthesis that are cytoprotectors for the gastric mucous membrane. Besides, NSAIDs cause disorders of microcirculation (causing edema) and stimulate cytokines production.
- ***Neprotoxicity*** of NSAIDs is found to inhibition of Pg synthesis in kidneys leading to disorders of microcirculation in kidneys, disorders of renal filtration

and edema development. NSAIDs also cause hypokalemia, hyponatremia and hyper-tension.

- ***Hyperuricemia*** is associated with urates refention in the body due to inhibition of their secretion in distal canals of the kidneys
- ***Inhibition of platelet aggregation*** and decrease of prothrombin formation in the liver cause bleedings (the anti-agregant effect)
- ***Disorders of the CNS*** (dizziness, headache, sleep disorders) are the result of penetration of NSAIDs to the brain and accumulation of their serotonin-like metabolites inside the CNS.

SYMPTOMATIC TREATMENT OF NSAIDs INTOXICATION

Symptom / Effect	***Treatment***
↓ Absorption, ↑ elimination	Washing of the stomach, enterosorption, "forced" diuresis
Acidosis	To make urine more alkaline
Convulsions	Diazepam
Coma	Ventilation of lungs, Furosemide, Dexamethasone, osmotic diuretics
Pulmonary edema	Nytroglycerin, Furosemide, Dopamine
Bradyarrhythmia	Dopamine
Gastric ulceration	Ranitidine, Misoprosfol, Lansoprazole

ASA, SALICYLATES. TOXIDYNAMICS

- Acute intoxication: abdominal pain, nausea, vomiting (with blood), bloody diarrhea; dizziness, disorders of hearing and vision, headache, insomnia, tremor, hyperventilation, hyperemia, hyperhydrosis, tachyarrhythmia, delirium; hypocalemia, hyponatremia, hypoprothrombinemia. In severe cases convulsions, coma, dehydration, shock, renal and hepatic failure, gastro-intestinal bleeding, ketoacidosis occur.
- Lethal outcome may be caused by heart failure, paralysis of respiration, brain edema.

CHRONIC INTOXICATION:

- Skin haemorrhages
- CNS disorders
- Acidosis
- Dehydration

THE MECHANISM OF THE TOXIC ACTION OF ASA

- Stimulation of the respiratory centre causes hyperventilation leading to respiratory alkalosis and further to metabolic acidosis (compensatory reaction) and dehydration.
- Disorders of oxidative phosphorilation processes lead to hypoglycemia, fever, tachycardia.
- Disorders of the coagulation factors activity in the liver lead to the so called

"haemorrhagic" syndrome. Besides, decrease of platelet aggregation helps this effect.

- Rey's syndrome – a strong renal and hepatic disorder caused by mitochondria damage.
- Formation of leukotrienes causes a bronchospasm and "aspirin-induced asthma"

SYMPTOMATIC TREATMENT OF INTOXICATION BY ASA

Symptom/Effect	Treatment
↓ Absorption, ↑ elimination	Washing of the stomach, vaselin oil, laxatives, activated charcoal, ascorbic acid
Acidosis	Sodium hydrocarbonate
"Aspirin" asthma	Zafirlukast, Montelukast
Convulsions	Diazepam
Coma	Ventilation of lungs, Furosemide, Dexamethasone, osmotic diuretics
Hypoglycemia	Glucose
Bleedings	Vitamine K

PREVENTION OF INTOXICATION

- Smoking, long-term administration provoke toxic effects of NSAIDs
- NSAIDs are contraindicated ***(strictly!)*** with anticoagulants, heparin, hypoglycemic diuretics, hypotensives, antidepressants, sulfonamides, other NSAIDs, glucocorticosteroids, alcohol.
- The groups of risk: old patients (older than 65), patients that have renal, hepatic or heart failure, hyponatremia, hypertension, dehydration, obesity, alcoholism.
- To take NSAIDs correctly is to drink with a lot of water avoiding direct irritation of the GIT

LECTURE 3
TOXICOLOGY OF MEDICINES AFFECTING EFFERENT INNERVATION

Normal functions of the efferent nerves are provided by such neurotransmitters (mediators) as acetylcholine, noradrena-line, adrenaline, dophamine. Medicines, which action is similar or opposite to these neurotransmitters, are called medicines of the mediator action or mainly affecting the efferent division of the nervous system (efferent innervation)

THE LOCALIZATION OF M, N-CHR

- M-ChR are located in organs,
- N-ChR are located in:
  - the ganglia
  - the adrenal medulla
  - in the carotid sinus of aorta

- in the skeletal muscles
- all ChR are also found in the CNS

☐ When using cholinergic medicines the effects connected with the stimulation of parasympathetic nerves dominate in the organism

CLASSIFICATION OF MEDICINES

Cholinomimetics:	Anticholineste-rase medicines:
1. M- cholinomimetics Pilocarpine Aceclydine	1. Reversible action Physostigmine Proserin Galantamine
2. N- cholinomimetics Lobeline Cititone	2. Irreversible action Armine
3. M, N – cholinomimetics Acetylcholine Carbocholine	

THE INTERVAL OF THERAPEUTIC AND TOXIC DOSES

Medicines	Therapeutic doses	Toxic doses	Lethal doses
Pilocarpine	local:1-6% 10 ml	–	
Aceclydine	subcutaneously: 4-12 mg	subcutaneously: > 12 mg	
Lobeline	i/v: 5-10 mg i/m: 10-20 mg	i/v: > 10 mg i/m: > 20 mg	
Cititone	i/v & i/m: 1-3 ml (0,15 %)	i/v & i/m: >3 ml (0.15%)	
Acetylcho-line	i/m: 0.05-0.3 g	i/m > 0.3 g	
Carbocho-line	internal: 1-3 mg subcutaneously: 0.5-1 mg	internal: > 3 mg h/i: > 1 mg	
Physostig-mine	subcutaneously: 0.5-1mg	h/i : > 1 mg	subcutaneously: 0.006-0.01g
Proserin	internal :15 – 50 mg subcutaneously: 10-20 mg	internal : >50мg subcutaneously: > 20мg	internal: 60 mg
Galanta-	subcutaneously: 10-20	subcutaneously: >20	

mine	mg	mg	
Ubretid	internal :0.5-1 mg i/m: 0.5 мg	internal: >1mg i/m: >0.5 mg	
Armine	local: 0.01%-10 ml	toxic	

THE MECHANISM OF TOXICODYNAMICS OF CHOLINOMIMETICS

Stimulation of M, N – cholinergic receptors of the whole number of organs and tissues of our organism

Symptoms of intoxication in overdosing of cholinomimetics

Organ	Toxic effect
Eye	Miosis (constriction of a pupil), spasm of accomodation (myopia or short-vision, or shortsightedness)
Bronchi	Bronchospasm, acute croup
Heart, vessels	Bradycardia, arrhythmia, arterial hypertension, cardiogenic shock, pulmonary edema
GIT	Hyperperistalsis (diarrhea, abdominal pains). Exacerbation of peptic ulcer, hyperacidic gastritis
Adrenal medulla	Increase of function (↑ adrenalin secretion)
Urinary bladder	Increase of the tone
Sphincters	Relaxation
Skeletal muscles	Increase of the tone, convulsive syndrome (particularly anticholinesterase medicines)
Exocrine glands	Salivary glands – hypersalivation Wet glands – ↑ sweat Digestive glands – ↑ of secretion
CNS	Stimulation
Skin	Often wet, pale

SYMPTOMS OF INTOXICATION BY N-CHOLINOMIMETICS:

- ❑ excitation
- ❑ tachycardia or bradycardia
- ❑ tremor
- ❑ paralysis of the muscle activity
- ❑ no eye reaction to light
- ❑ normal peristalsis

TOXICOKINETICS OF CHOLINOMIMETICS

Acetylcholine	The effect is short and develops quickly. It penetrates through the BBB poorly (does not act to the CNS)
Carbocholine	Is more active than acetylcholine, acts for a long time
Aceclydine	Is well absorbed by any route of administration (including conjunctival). Good penetration through the BBB
Pilocarpine	Only local administration, doesnot have the systemic action in intraconjunctive administration
Lobeline	I/v effect is stronger than i/m. Causes apnea and bradycardia in rapid introduction
Cititone	Is equally effective in both ways of administration (i/m, i/v)
Physostigmine, galantamine	Are well absorbed and penetrate through biomembranes, BBB (have a marked effect on the CNS)
Proserin, Ubretid	Penetrate poorly through the BBB
Armine	Is used topically. One should avoid drug contact with the tear canals (may develop the systemic action)

TREATMENT OF INTOXICATION BY CHOLINOMIMETICS

ANTIDOTES AND ANTAGONISTS

As antidotes such M-cholinoblockers **Atropine, Aprofen, Metacin** are used
The basis of the antidote effect is a pharmacological antagonism.
M-cholinoblockers in this case are the medicines of ethiotropic treatment.
In case of intoxications by **anticholinesterase** medicines (especially irreversible acting ones) ***reactivators of cholinesterase*** are used as specific antidotes.

THE MECHANISM OF ACTION OF REACTIVATORS OF CHOLINESTERASE

Being strong nucleophilic compounds, they selectively act against toxic agents, and it leads to their displacement from binding with the enzyme and restore its activity

CHOLINESTERASE REACTIVATORS:

- Dipiroxim
- Alloxim
- Izonitrozine
- Dietixim

Biochemical antagonism is on the basis of the antidote effect of cholinesterase reactivators.

CLASSIFICATION OF M- CHOLINOBLOCKERS

Ones of the plant origin	**Synthetic ones**
Atropine sulphate Homatropine hydrobromide Platyphyllin hydrotartrate Scopolamine hydrochloride	Ipratropium bromide Methacine iodide Pirenzepine Tropicamide Aprofen Buscopan

THE INTERVAL OF THERAPEUTIC AND TOXIC DOSES

Medicines	Therapeutic doses	Toxic doses	Lethal doses
Atropine	Internal, subcutaneously: 1-3 mg	Internal, subcuta-neously: > 3 mg	internal: 10-60 mg
Scopolamine	Internal, subcutaneously : 0.5-1.5 mg	internal subcuta-neously: > 1.5 мg	internal: 0.1 g
Homatropine	local: 0.25%-1% 10 ml		
Platyphyllin	Internal, subcutaneously: 0.01-0.03 g	internal & subcuta-neously: > 0.03 g	
Aprofen	internal: 0.03-0,1 g i/m: 0.02-0.06 g	internal: > 0.1 g i/m: > 0.06 g	
Methacine	internal: 5-1.5 mg subcutaneously, i/m: 2-6 mg	internal: >1.5 mg h/i,i/m: > 6 mg	
Buscopan	internal: 0.01-0.1 g subcutaneously, i/m: 0.02-0.04 g	internal: > 0.1 g subcutaneously, i/m: > 0.04 g	
Pirenzepin	internal: 0.05-0.15 g subcutaneously, i/m: 0.01-0.03 g	internal: > 0.15 g subcutaneously, i/m: > 0.03 g	

THE MECHANISM OF TOXICODYNAMICS OF M – CHOLINOBLOCKERS

Is connected with prolonged and marked blockade of M-cholinoreceptors and, thus, decrease their interaction with acetylcholine.

SYMPTOMS OF INTOXICATION BY M – CHOLINOBLOCKERS

Organ	Toxic effect
Eye	Mydriasis (the dilation of pupil), paralysis of accommodation, diplopia
Bronchi	Dilation of bronchi (bronchiectasis)
Heart, vessels	Tachycardia, hypertension, pain behind the breast. Acute heart failure (in elderly patients)
GIT	Peristalsis is decreased, constipation
Bladder	Urinary retention (we have a relaxation of the smooth muscles of bladder and gall bladder and spasm of the sphincters, and it leads to difficult urination and to anureses)
Sphincters	Spasm
Skeletal muscles	Relaxation (particularly Scopolamine) Hyperkinesis are possible
Exocrine glands	Decrease in secretion activity of salivary, lacrimal, sweat, bronchial and digestive glands
CNS	Cholinolytic psychosis (anxiety, hallucinations, convulsions). Respiratory centre depression. Coma. Cognitive disorders
Skin	Dry skin, redness

TOXICOKINETICS

- Symptoms of intoxication by **M – cholinoblockers** can be delayed in time due to decrease of the intestinal motility. It explains the duration of intoxication, which can last up to 3-5 days or more
- All anticholinergic medicines can accumulate in the intestine.
- Atropine, Scopolamine and Platyphyllin penetrate well through the BBB, have the effect on the CNS and are very toxic.
- Metacine, Buscopan and Pirenzepin penetrate through the BBB badly and have no effect on the CNS and are less toxic

CLASSIFICATION OF GANGLIONIC BLOCKERS & MUSCLE RELAXANTS

Ganglionic blockers	Muscle relaxants
Azamethonium bromide (Pentamine) Dimecoline iodide Hexamethonium benzosulphonate Pachicarpine hydroiodide	***Non-depolarizing:*** Tubocurarine chloride Diplacine dichloride Mellictin Pipecuronium bromide ***Depolarizing:*** Suxamethonium iodide (Dithilin)

THE INTERVAL OF THERAPEUTIC AND TOXIC DOSES

Medicine	Therapeutic doses	Toxic doses
Hexamethonium benzosulphonate	internal: 0.3-0.9 g subcutaneously: 0.075-0.3 g	internal: > 1.0 g
Azamethonium bromide	i/m: 0.15-0.45 g	i/m: > 0.45
Dimecoline iodide	internal: 0.05-0.1 g	internal: > 0.1 g
Trepirium iodide	i/v: 0.04-0.08 g	
Pachicarpine hydroiodide	internal: 0,2-0,6 g subcutaneously: 0.15-0.45 g	internal: > 0.6 g subcutaneously: > 0.45 g
Tubocurarine chloride	i/v:15-25 mg	i/v: > 25 mg
Diplacine	i/v:0.1-0.2 g	
Mellictin	internal: 0.02-0.1 g	internal: > 0.1 g
Dithiline	i/v:1.5-2 mg/kg	

THE MECHANISM OF THE TOXIC ACTION OF GANGLIONIC BLOCKERS

Ganglionic blockers are similar to ACh by their chemical structure. As a result of their competitive antagonism with ACh for N-ChR of the sympathetic and parasympathetic ganglia they block these receptors and interrupt the nerve impulse transmission through ganglia. While introducing ganglionic blockers the "pharmacological denervation" of the internal organs occurs.

SYMPTOMS OF INTOXICATION BY GANGLIONIC BLOCKERS

Organ	Toxic effect
Eye	Mydriasis Paralysis of accommodation
Heart Vessels	Tachycardia Orthostatic collapse
GIT	Atony of the intestine (up to its paralysis)
Bladder	Atony with anuria
Smooth muscles	Relaxation

High doses of ganglionic blockers can lead to development of toxic effects similar to intoxication by M-cholinoblockers.

TOXICODYNAMICS OF MUSCLE RELAXANTS

Myorelaxants cause relaxation of the skeletal muscles in a certain sequence. At first, the paralysis of small muscles of face, neck, fingers and toes and speaking disorders develop. Then the muscles of extremities, trunk, muscles of abdomen and, at last, diaphragm stop functioning consistently. But consciousness and sensitivity are not disturbed. Death can be caused by hypoxia (diaphragm and breathing muscles stop working). The recovery of the muscle tone occurs in the reverse order.

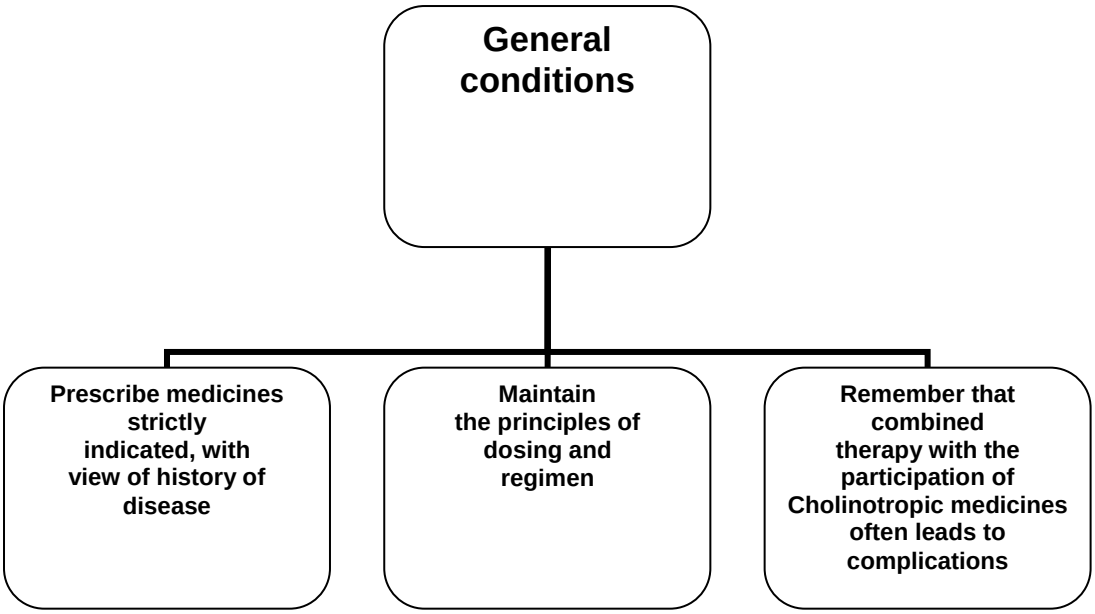
SYMPTOMS OF INTOXICATION BY MUSCLE RELAXANTS

- ❑ Skeletal muscles— relaxation
- ❑ Respiratory muscles — relaxation, asphyxia
- ❑ In high doses they can act on M-cholinoreceptors

TREATMENT OF INTOXICATION BY CHOLINOBLOCKERS

- ❑ Anticholinesterase medicines are used (Physostigmine, Galantamine, Proserin).
- ❑ The basis of the antidote effect of these medicines is pharmacological antagonism.
- ❑ Neostigmine methylsulphate is an antidote in intoxication by ganglionic blockers.
- ❑ Reversible-acting anticholinesterase medi-cines are antidotes in intoxication by non-depolarizing muscle relaxants.
- ❑ There are no antidotes for depolarizing muscle relaxants

PREVENTION OF INTOXICATION CAUSED BY CHOLINOTROPIC MEDICINES



The toxic effects of cholinomimetics may increase because of concomitant diseases:

Diseases of:

1. the respiratory tract (bronchial asthma)
2. the CVS (arrhythmia, angina pectoris, MI)
3. epilepsy
4. hyperkinesis
5. the gastrointestinal tract (peptic ulcer, bleeding in the stomach, intestine)
6. during pregnancy except of labour induction (Aceclidine) these medicines are prescribed for health

Prescription of M-cholinoblockers are dangerous in the following diseases:

1. the CVS (arrhythmia, MI)
2. the GIT (ulcerative colitis)
3. Hyperthyroidism
4. Adenoma of prostate

Ganglionic blockers are not used in:

1. the CVS (MI in the acute stage, arrhythmia, hypotension)
2. Liver disease
3. Adenoma of the prostate
4. Degenerative changes in the CNS

Muscle relaxants are dangerous in myasthenia, liver and kidney diseases.

Factor that increases toxicity of medicines is an elder and children age.

ADRENOMIMETICS

Group	Medicines
α_1-adrenomimetics	Norepinephrine, Mesatone
α_2-adrenomimetics	Clonidine
β_1-adrenomimetics	Dobutamine
β_2-adrenomimetics	Fenoterol, Salbutamol
β 1,2-adrenomimetics	Isoprenaline (Isadrin)
α + β-adrenomimetics	Adrenaline
Sympathomimetics	Ephedrine

INTERVAL OF THERAPEUTIC AND TOXIC DOSES

Medicine	Therapeutic doses	Toxic doses	Lethal doses
Adrenaline	subcutaneously:1-5 ml (0.1%)	subcutaneously: > 5 ml (0.1%)	i/v: 5-10 mg
Ephedrine	Internal, subcutaneous-ly: 0.05-0.15 g	Internal; subcutaneously: > 0.15 g	internal: 1-2 g
Orciprenaline	internal: 0.02-0.08 g	internal: > 0.08 g	
Isadrin	internal: 5-20 mg inhalation: 0.2-0.8 ml	internal: > 20 mg	
Phenoterol	Inhalation: 0.2-0.6 mg	Inhalation: > 0.6 mg	
Salbutamol	Inhalation: 0.1-0.6 mg	Inhalation: > 0.6 mg	
Dobutamine	i/v: 0.25 g	i/v: > 0.25 g	
Mesatone	internal:0.03-0.15 g Subcutaneously; i/m: 0.01-0.05 g i/v: 5-25 mg	internal: > 0.15 g Subcutaneously; i/m: > 0.05 g i/v: > 25 mg	
Norepinephrine	i/v: 0,2%-2 ml		
Clonidine	internal: 0.075-0.45 mg	internal: >0.45 mg	

THE MECHANISM OF THE TOXIC ACTION OF ADRENOMIMETICS

Medicines of this group stimulate AR:

- α_1- adrenomimetics stimulate α_1-AR of vessels;
- α_2- adrenomimetics stimulate α_2-AR of the vasomotor centre and sympathetic nerve fibres;
- β_1-adrenomimetics stimulate β_1-AR of the myocardium;
- β_2-adrenomimetics stimulate β_2-AR of the bronchi, uterus and vessels;
- β_1+β_2-adrenomimetics stimulate β_1- and β_2-AR of the myocardium, bronchi, uterus, vessels;
- α_1, α_2, β_1, β_2- adrenomimetics stimulate α_1-, α_2-, β_1-, β_2-AR.
- Ephedrine hydrochloride is an indirect-acting adrenomimetic (sympathomimetic) that suppresses the activity of MAO and COMT and the recapture (re-uptake) of catecholamines and it leads to the increase of the neurotransmitter's concentration in the synaptic cleft.

SYMPTOMS OF INTOXICATION BY ADRENOMIMETICS

Organ	Toxic effect
Heart, vessels	Tachyarrhythmia, hypertension, myocardium disorders up to MI
CNS	Stimulation, tremor, toxic psychosis
Metabolic imbalance	Hyperglycemia, hypokalemia, acidosis
Eye	Mydriasis
Bronchi	Dilation of bronchi (Bronchiectasis)
GIT	Peristalsis depression
Skeletal muscles	Increase of the tone (tremor)
Urinary bladder	Increase of the tone of the urethra sphincter muscle. Decrease of diuresis

SYMPTOMS OF INTOXICATION BY CLONIDINE

- Hypotension
- Reflex tachycardia
- Metabolic acidosis
- Circulatory hypoxia
- Cardiogenic shock
- Cerebral ischemia
- Possible: coma, apnea
- In all stages of intoxication: severe weakness, headache, heaviness in the head, visual disorders, hyperhydrosis of the skin, disorders of cognitive function

TREATMENT OF INTOXICATION BY CLONIDINE

- **Bradycardia** – β_1-adrenomimetics, antiarrhythmic medicines are used

- **Hypotension** – α_1-adrenomimetics, adrenaline, dopamine are used
- **With consciousness depression** give Na-loxone (an antagonist of Clonidine), 40% Glucose solution, the infusion of saline and ascorbic acid
- **With respiratory depression** give oxygen

Atropine and Prednisolone are also used in the treatment of intoxication by Clonidine

TREATMENT OF INTOXICATION BY ADRENOMIMETICS

There are no specific antidotes, only symptomatic and pathogenic therapy is used.

For removal:

- Arrhythmias - β-blockers, calcium antagonists, antiarrhythmic medicines are used
- Hypertension – antihypertensive medicines are used
- Excitation – benzodiazepines are used
- Inhibition of the intestinal peristalsis – Metoclopramide

When treating intoxications by adrenomimetics cholinomimetics are used (the physiological antagonism)

FACTORS ASSISTING TOXICITY OF ADRENOMIMETICS

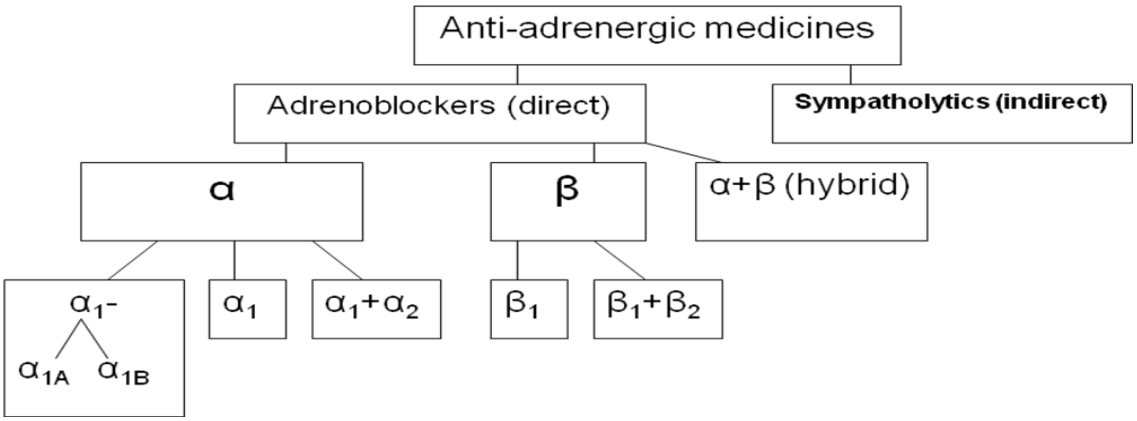
- In childhood and old age
- In concomitant diseases:

- Hypertension
- Angina pectoris
- Atherosclerosis
- Thyrotoxicosis
- Diabetes mellitus

All medicines in this group have a little interval of the therapeutic action, therefore, an important thing warning intoxications with these medicines is the principle of dosing in the treatment by adrenomimetics

ANTI-ADRENERGIC MEDICINES (ADRENOBLOCKERS AND SYMPATHOLYTICS)

ADRENOBLOCKERS



ADRENOBLOCKERS

Group	Medicines
a1-adrenoblockers	Prazosine, Terazosine, Doxazosine, Tamsulosine
a1+2- adrenoblockers	Dihydroergotamine, Nicergoline, Phentolamine, Pirroxan, Proroxan
β1- adrenoblockers	Metoprolol, Betaxolol, Talinolol, Bisoprolol, Atenolol
β1+2-adrenoblockers	Nadolol, Propranolol, Oxprenolol, Sotalol
Hybrid [a+β]-adreno- blockers	Labetolol
Sympatholytics	Reserpine

THE INTERVAL OF THERAPEUTIC AND TOXIC DOSES

Medicine	**Therapeutic doses**	**Toxic doses**
Dihydroergotamine	internal: 2.5-5 mg	internal: > 5 mg
Dihydroergotoxine	internal: 70 drops (0,1%)	internal:> 70 drops
Nicergoline	internal: 0.01-0.03 g	internal: > 0.03 g
Phentolamine	internal: 0.05-0.5 g	internal: > 0.5 g
Pirroxan	internal: 0.06-0.18 g	internal: > 0.18g
Prazosine	internal: 0.5-4 mg	internal: > 4 mg
Terazosine	internal: 1-10 mg	internal: > 10 mg
Doxazosine	internal: 1-16 mg	internal: > 16 mg
Tamsulosine	internal: 0.4 mg	
Medicine	Therapeutic doses	Toxic doses
Atenolol	internal: 0.05-0.2 g	internal: > 0.2 g
Metoprolol	internal: 0.1-0.6 g	internal: > 0.6 g
Talinolol	internal: 0.05-0.3 g	internal: > 0.3 g
Bisoprolol	internal: 5 mg	

Anapriline	internal: 0.02-0.08 g	internal: > 0.08 g
Oxprenolol	internal: 0.02-0.12 g	internal: > 0.12 g
Nadolol	internal: 0.04-0.24 g	internal: > 0.24 g
Labetolol	internal: 0.1-1.0 g	internal: > 1.0 g
Bopindolol	internal: 0.001-0.005 g	internal: > 0.005 g
Sotalol	internal: 0.04-0.48 g	internal: > 0.48 g
Reserpine	internal: 0.25-10 mg	internal: > 10 mg

THE MECHANISM OF THE TOXIC ACTION OF ANTI-ADRENERGIC MEDICINES

They block adrenoreceptors inhibiting neurotransmission in sympathetic nerves.

Organ	Toxic effect
Heart, vessels	Arrhythmia, cardiac conductivity disorders (> β-adrenoblockers), hypotension, cardiogenic shock
Bronchi	Bronchospasm (β-adrenoblockers, Labetolol, Reserpine). Development of hypoxia
GIT	Nausea, vomiting, diarrhea. Peristalsis is normal
Metabolic disorders	Hyperglycemia, hypokalemia (β-adrenoblockers)
CNS	Dizziness, coma, convulsions (β-adrenoblockers), drowsiness, parkinsonism (Reserpine)
Skin	Wet skin (β-adrenoblockers), redness and itching of the skin
Other	Weakness and fatigue, dry mouth (β-adrenoblockers)

TREATMENT OF INTOXICATION BY ANTI-ADRENERGIC MEDICINES

- **Arrhythmia –** anti-arrhythmic medicines
- **Cardiogenic shock** – cardiostimulators
- **Hypotension** – Adrenaline, Norepinephrine, Dopamine
- **Bronchospasm** – Atropine sulphate, Aminophylline, β2-adrenomimetics
- **GIT disorders** – antiemetic medicines, anticholinergic medicines
- **Hypoglycemia** – Glucagon, Adrenaline, Glucose
- **Hypokalemia** – potassium-containing medicines
- **Convulsions** - Diazepam, anticonvulsants
- **Extrapyramidal disorders** - Trihexyphenidyl, Diphenyltropine

FACTORS ASSISTING TOXICITY OF ANTI-ADRENERGIC MEDICINES

- Age
- Pregnancy
- Diseases of the GIT and kidney
- Sclerotic changes in the organs and vessels
- Severe heart diseases
- Cerebral circulation disorders
- Diabetes mellitus, bronchial asthma, chronic pulmonary diseases (β-adreno-blockers)

LECTURE 4:
TOXICOLOGY OF MEDICINES, AFFECTING THE CARDIO-VASCULAR SYSTEM (CARDIAC GLYCOSIDES, ANTI-ANGINAL MEDICINES, ANTI-HYPERTENSIVE DRUGS, ANTI-ARRHYTHMIC DRUGS)

CARDIAC GLYCOSIDES (CG)

Cardiac glycosides are basic medicines for treatment of heart failure. They increase productivity of myocardium, provide effective and optimal function of the heart.

CLASSIFICATION AND MEDICINES

Medicines containing Digitalis glycosides	**Medicines containing Strophanthus glycosides**	**Medicines containing glycosides of Convallaria, Adonis*, Scilla maritima**, combined agents*** **
Digoxin Lantoside Digitoxin Cordigit	Strophanthine K	Corglycon Adoniside* Meproscillarin** Cardiovalen***

INTERVAL OF TOXIC ACTION OF GC

Medicine	**Interval of the toxic action/toxic dose**
Digitoxin	0.5 mg
Digoxin	2.0-4.0 ng/ml

TOXICODYNAMIC OF CG

- The cardiotoxic effect: (negative chronotropic and dromotropic effect, all kinds of the heart rate disorders), ventricular extrasystoles (tachycardia up to the total heart blockade, fibrillation of antricles and ventricles); hypotension. Death the cause of is heart stoppage and asphyxia in 30 minutes after i/v injection of toxic dose.

- ❑ The neurotoxic effect: headache, dizziness, ataxia, excitement, convulsions, delirium, disorders of respiration, cyanosis.
- ❑ The gastrotoxic effect: nausea, vomiting (sometimes with blood), abdominal pain, diarrhea.
- ❑ Antidiuretic effect: edema, water retention

DIFFERENCES BETWEEN ACUTE AND CHRONIC CG INTOXICATION

Criteria	**Acute intoxication**	**Chronic intoxication**
Type of patients	Patients are healthy, without the heart disease	Patients have the heart diseases
Symptoms	Nausea, vomiting, diarrhea	Anorexia, vomiting, nausea, headache, faitigue, drowsiness, paresthesia, neuritis, disorientation, hallucinations, delirium, convulsions, eyesight disorders (double vision, color perception), skin rash
ECG (electroncardiogram) markers	Supraventricular arrhythmia with the heart blockade, bradycardia	All types of arrhythmias: especially non-paroxismal tachycardia, atrial tachycardia
Concentration of potassium in the blood	Normal or increased	Normal or decreased

THE MECHANISM OF TOXICODYNAMIC OF CG

Inhibition of sulphhydryl-groups of Na+/K+ - ATPase

Stimulation of the intracellular exchange of Na+/Ca2+	**Inhibition of the intracellular potassium exchange**
✓ Delayed postdepolarization → Tachyarrhythmia	Disorders in the conductive system → Ventricular tachycardia
✓ Disorders of automatism of atrial conduction → atrial bradycardia	Increased automatism → Ventricular tachycardia

1. ***Disorders of cardiac conduction*** is the result of the functional state changes at cell membranes of cardiomyocytes: slowdown of repolarisation alters the process of the final repolarization onset
2. ***Bradycardia, the antrioventricular blockade*** are caused by stimulation of the vagus nerve with CG
3. ***Ischemia of myocardium*** is caused by c0ronary vessels spasm

FACTORS ASSISTING TOXICITY OF CG

1. ***Increased cardiosensitivity:***
   - ❑ Acute hypoxia
   - ❑ Electrolyte disorders: hypokalemia, hypernatremia, hypercalcemia, hypermagnesemia
   - ❑ Respiratory alkalosis
   - ❑ Ischemia of the myocardium (acute stage of myocardial infarction), myocarditis
   - ❑ The increased tone of the sympathetic nervous system
   - ❑ Aged people
   - ❑ acidosis
   - ❑ hypothyroidism
2. ***Increased concentration of CG in the blood:***
   - ❑ Overdose of CG
   - ❑ Disorders of the renal or liver function

SYMPTOMS OF OVERDOSE

Symptoms	Pharmacotherapy
Sinal bradicardia, atrioventricular blockade of the II and III stage	Atropine solution (0,5 mg i/v). If necessary, take each 10-15 minutes repetitively
Ventricular arrhythmia	Potassium-containing medicines (Potassium chloride, Potassium citrate, Potassium adipinate 2-4 g/day)
Extrasystolia	Anti-arrhythmic medicines : Lidocain, Xylocain (at the very beginning 50-100 mg i/v slowly, their – infusion 1-2 mg/min)
Supraventricular tachyarrhythmia with atrioventricular blockade, ventricular arrhythmias	Phenitoin (50-100 mg i/v slowly, after the dose should be increased up to 1 g per day; the maintainance dose is 0.3-0.6 g per day)
Ventricular arrhythmia	Lidocain, Phenitoin
Vomiting, excitement	Chlorpromazine

TREATMENT OF INTOXICATION

- ❑ Potassium-containing medicines (antagonists of toxic effects of CG)
- ❑ Unithiol, sulfur-containing aminoacids (Cystein). They are donores of SH-groups

PREVENTION OF INTOXICATION

- ❑ Risk of CG intoxication decreases when using diet, rich in potassium salts

(dried apricots, fruit juices, bananas) or taking potassium-containing medicines: Panangin, Asparkam, Potassium chloride.

- Combined intake of Doxorubicin and CG decreases the risk of toxic cardiomyopathy in patients taking Doxorubicin.
- For prevention of intoxication by CG Phenytoin, Potassium citrate, Atropine, Riboxin are used.
- Strophanthin K should be injected slowly (over 5-6 min.) avoiding the cardiogenic shock development

TOXICOKINETICS OF CG

Factors affecting toxicokinetics:

Absorption. Absorption decreases in case of the food intake at the same time, in malabsorption, in case of combination to antiacids and medicines inhibiting the gastrointestinal motility.

*Distribution. The v*olume of distribution decreases in case of kidney diseases, hypothyroidism, therapy by Quinidine, in aged people → all factors increase the concentration of CG .

Pregnancy. It is known that 8.9 mg of Digitoxin caused intoxication of mother and fetus.

MEDICINES AFFECTING TOXICOKINETICS

- Ones decreasing absorption: Activated charcoal, antiacids, Cholestiramine, Colestipol, Cyclophosphamide, Doxorubicin, Metoclopramide, Neomycin, Sulfasalasine.
- Ones increasing absorption: antibiotics, cholinoblockers.
- Ones inhibiting the plasma proteins binding: Clofibrate, Phenobarbital, Phenylbutazone, Prazosin, sulfonamides, Tolbutamide, Varfarin.
- Ones stimulating metabolism in the liver: Phenobarbital, Phenylbutazone, Phenytoin, Rifampicin.
- Ones stimulating the renal excretion: Hydralasine, Levodopa, Nitroprusside.
- Ones inhibiting the renal excretion: Quinidine, Spironolactone, Triamterene, Trimetoprim, Verapamil.

ANTI-ANGINAL MEDICINES

Antianginal medicines are medicines that decrease oxygen consumption by the myocardium and increase the myocardium supply with oxygen, optimize energy metabolism in cardiac myocytes. These agents are used for treatment of angina pectoris (ischemic heart disease) and myocardial infarction

CLASSIFICATION OF MEDICINES

Nitrovasodilators (organic nitrates)	Calcium canals blockers	Different medicines
Glycerol trinitrate Isosorbide dinitrate Isosorbide mononitrate	Nifedipine Isradipine Amiodaron Amlodipine Verapamil Dilthiazem	Amiodaron

Medicines decreasing oxygen consumption by the myocardium β-adrenoblockers (β1, β1+ β2*)	Medicines increasing the oxygen delivery to the myocardium (coronarolytics)	Medicines improving the metabolism in the myocardium
Atenolol Metoprolol Bisoprolol Propranolol*	Dipyridamol	Trimethasidine Inosine

THE INTERVAL OF THE THERAPEUTIC AND THE TOXIC ACTION, LETHAL DOSES

Medicine	Interval of the therapeutic action	Interval of the toxic action	Lethal doses
Glycerol trinitrate		> 20 mcg/kg	
Talinolol			1.5 g
Dipyridamol	75-100 mg	200-400 mg	
Dilthiazem		720-5880 mg	
Nifedipine		280-800 mg	
Verapamil		960mg-9.6 g	

NITROVASODILATORS
TOXICODYNAMIC

- Headache, dizziness;
- Reddening of the skin, mainly those of the upper half of the body;
- Nausea, vomiting;
- Acute decrease of BP until the collapse;
- Reflex tachycardia;
- Coma with cyanosis and respiratory paralysis;
- Blood has a chocolate shade (methehaemoglobinemia)

THE MECHANISM OF TOXICODYNAMIC OF ORGANIC NITRATES

↓ of BP is **the** consequence of vasodilation induced by NO.

Headache is a response to stimulation of structures with pain sensitivity: arte-

ries, veins, meninges, nerves, intracerebral sympathetic plexus, due to an increase or decrease of ICP, edema, inflammation and irritation of the meninges.

Methehaemoglobinemia is the result of failure of methaemoglobinreductase.

FACTORS ASSISTING TOXICITY OF NITROVASODILATORS:

- Acute decrease of BP, orthostatic hypotension, tachycardia, caused by Glycerol trinitrate, often appears in case of taking a medicines when standing. During the treatment by Glycerol trinitrate it is not allowed to drink alcohol because acute heart failure and a collapse (up to death) may develop
- Severe hypotension, tachycardia is possible in combination of nitrovasodilators with narcotic analgesics, Levodopa, Bromocriptine, neuroleptics, Amantadine, tricycle antidepressants, Procainamide, Quinidine sulfate, as well as in the case of the combination with alcohol.
- Combination with Viagra can also lead to an acute decrease of BP, collapse, myocardial infarction

PREVENTION OF NITRATE INTOXICATION

- Headache is weakened by the combination of nitrovasodilators with the medicines containing menthol (validol, etc.), acetylsalicylic acid, β-blockers.
- The decrease of BP, tachycardia are less pronounced under the condition of taking nitrovasodilators in a lying or sitting position with legs elevated.

WHAT TO DO?

With the i/v administration the further introduction of the medicines is stopped. With transdermal administration remove the rest of an ointment or plaster. Prescribe Activated charcoal, gastric irrigation, followed by the prescription of salted laxatives.

Symptoms	Pharmacotherapy
Hypotension, collapse	Epinephrine or norepinephrine administration
Methehaemoglobinemia	1 ml of 1% solution of Methylene blue with i/v administration per 1 kg of the body weight (an average of 5-6 ml) with Glucose and Ascorbic acid
Depression and respiratory paralysis	Resuscitation, forced diuresis, hemodialysis, exchanged transfusion

β-ADRENOBLOCKERS

TOXICODYNAMICS

- From the CVS: Slowing down of the sinus rhythm, ↓ the strength of heart contractions (Propranolol), hypotension, the low cardiac output syndrome (Propranolol), atrioventricular blockade, disorders of intraventricular pressure, asystole (Atenolol, Metoprolol); ventricular tachyarrhythmia (Sotalol).

- From the CNS: weakness, headache, loss of consciousness, which is associated with worsening of the cerebral blood flow due to acute decrease of BP and a direct influence on the activity of neurons in the brain (Propranolol), depression, hallucinations, excitement, convulsions, vision disorders (Oxprenolol, Sotalol).
- From the respiratory system: respiratory depression and apnea (Propranolol, Oxprenolol); bronchospasm with dyspnea, cyanosis (Propranolol, Oxprenolol).
- Other: hypoglycemia, acidosis (Propranolol).

TOXIC EFFECTS OF β-ADRENOBLOCKERS

Cardiac toxic effects	Extracardiac toxic effects
Sinus bradycardia	Severe hypoglycemia
Hypotension	Decrease of secretion of renin by the kidneys
Blocks of varying degrees: intraventricular atrioventricular blockade, extrasystole, asystole	Hyperkalemia, respiratory depres-sion, neuropsychiatric disorders
Disorders of the systemic hemody-namic: decrease of the cardiac output and increase of TPVR in the early and later phases of intoxication	Marbling of the skin (the skin is cold, wet), decreased blood flow to the extremities, decreased body temperature, oliguria

THE MECHANISM OF TOXICODYNAMICS OF B-ADRENOBLOCKERS

- The mechanism of the general toxic effect of β-adrenoblockers is a triad of mechanisms: the blockade of adrenergic receptors, the membrano derpessive action, blockade of the calcium channel.
- The weakening of the heart work is the result of reducing sympathetic effects with prolonged use. Many of the toxic effects of β-blockers are because of blockade of β2-adrenergic receptors.
- Bradycardia is the result of reducing the entry of calcium in pacemaker cells of the conduction system of the blood, weakening of sympathetic influences.
- Hypoglycemia is the result of inhibition of glycogenolysis.
- Bronchospasm, conduction disturbances of the heart is the result of the weakening of sympathadrenalic influences.

PREVENTION OF INTOXICATION of β-ADRENOBLOCKERS

- In order to prevent a bronchospasm caused by β-adrenoblockers in patients with a tendency to bronchial obstruction, treatment should be carried out with small doses of cardioselective medicines (Atenolol, Metoprolol, Talinolol, Acebutolol) in combination with aerosols of bronchodilators (Salbutamol, Fenoterol and Terbutaline).
- The development of heart failure while taking β-adrenoblockers can be pre-

vented by taking Digoxin and diuretics.

- β-adrenoblockers possessing the intrinsic sympathomimetic activity (Acebutolol, Oxprenolol, Pindolol), are less dangerous for development of bradycardia, conduction abnormalities, the cardioselective ones (Atenolol, Metoprolol, Acebutolol) - in bronchial obstruction.
- Pregnant women are recommended to stop taking Propranolol for 2-3 days before labour

TREATMENT OF INTOXICATION

Symptoms	Pharmacotherapy
Hypotension	Infusion therapy, symptomatic medicines: Dopamine, Epinephrine, Isoproterenol
Bradycardia	Atropine, Calcium chloride
Ventricular tachyarrhythmias	Lidocaine, cardioversion using direct current
Bronchospasm	Epinephrine

ANTIDOTES AND ANTAGONISTS

- Antagonists of β-adrenoblockers are M-cholinoblockers (Atropine, etc.), β-adrenoceptor agonists (Isoprenaline), glucagon, calcium-containing medicines.
- The mechanism of action of glucagon is due to the increased level of cAMP through the non-catecholamine mechanism and can cause severe chronotropic and inotropic effects

CALCIUM CANALS BLOCKERS

TOXICODYNAMIC

- CNS depression, respiratory depression
- Nausea, vomiting;
- The skin and mucous membranes become dry and pale;
- Pupils are dilated with no reaction to light;
- The tone of the skeletal muscle is reduced;
- Motility of intestine is decreased, there may be oliguria;
- Defective the colour vision ("silver" paint of objects), associated with the change of the blood flow in the retina;
- Slowing of the sinus rhythm, marked bradycardia, disorders of AV conduction of excitation, weakening of the strength of heart contractions, which shows with decrease of the blood minute volume, hypotension, early collapse, oliguria;
- Hyperglycemia;
- Psychosis (Nifedipine), Diltiazem;
- Hypocalcemia

THE SEVERITY OF INTOXICATION BY CALCIUM CANALS BLOCKERS

The degree of intoxication	Symptoms
Light	Sinus bradycardia, moderate hypotension (BP syst. up to 100 mm. Hg. column), stable condition, a clear conscience
Average	Hypotension (80 mm. Hg column and below), marked sinus bradicardia, arrhythmias
Sever	Complete AV blockade, cerebral blood flow disorders, psychosis

THE MECHANISM OF TOXICODYNAMICS OF CALCIUM CANALS BLOCKERS

- Decrease of BP due to the blockade of slow calcium canals resulting in the expressive vasodilating effect, hypo-tension, which is the cause of dizziness, heaviness in the head, tinnitus, fainting.
- Renal hemodynamic disorders and development of oliguria is a consequence of an disbalance between endogenous vasoconstrictors (renin) and vasodilators (prostaglandin E2) caused by Calcium canals blockers.
- Development of psychosis because of the disorders of synthesis and release of neurotransmitters of the CNS, as well as changes in the activity of the enzyme, involved in the synthesis of dopamine.
- Changes in colour sensation due to disorders in the blood flow in the retina.
- Hyperglycemia is the consequence of blocking of the calcium canals in β-cells of the pancreas

TREATMENT OF INTOXICATION

- Deliver the patient to the intensive care unit and carry out continuously monitoring of ECG.
- Clear gastrointestinal tract by washing out and oral administration of repeated doses of activated charcoal, laxatives.

Symptoms	Therapy
Hypotension	Epinephrine, Norepinephrine, Dopamine or Glucagon
Convulsions	Diazepam 5-10 mg i/v, Phenytoin i/v slowly
Arrhythmias: sinus or node bradyarrhythmia	Atropine 0.5 mg i/v, Izopreterenol 1-10 mcg / min i/v, ventricular stimulation, Calcium chloride 1 g (10 ml of 10% sol.) or Calcium gluconate 2-3 g (30 ml of 10% sol.) i/v for 5 min, 0.9% of Sodium chloride 200 ml i/v every 10 minutes up to 1-2 l

DIPYRIDAMOLE
TOXICODYNAMICS

- Headache, dizziness, ringing in the head;
- Paresthesia, myalgia;
- Hypotension;
- "Steal syndrome";
- Nausea, vomiting

THE MECHANISM OF TOXICODYNAMICS OF DIPYRIDAMOLE

"Steal syndrome" is the consequence of dilation of unaffected vessel areas of the myocardium to the outflow of the blood from the affected areas

FACTORS AFFECTING TOXICOKINETICS:

"Steal syndrome" occurs more often in atherosclerosis of coronary vessels.

During administration of dipyridamole one should avoid drinking tea and coffee. Dipyridamole increases the effect of other antithrombotic medicines, the toxic effect can be increased in combination with antibiotics of penicillin group, cephalosporins, tetracyclines, chloramphenicols.

ANTIHYPERTENSIVE MEDICINES

Antihypertensive medicines are medicines that decrease BP and used to treat hypertension or symptomatic hypertension

CLASSIFICATION OF MEDICINES

Medicines decreasing the activity of the nervous system sympathetic part			
α_2-adrenomimetics	***Sympatholytics***	***β_1-adrenoblockers , $\beta_1+\beta_2$-adrenoblockers ****	***α_1-adrenoblockers, $\alpha+\beta$ - adrenoblockers****
Clonidine hydrochloride	Reserpine	Propranolol * Atenolol	Prazosine Labethalol*

Peripheral vasodilators	***ACE inhibitors***	***Antagonists of calcium ions, spasmolytics****	
Hydralasine h/chl. Diazoxide Sodium nitroprusside	Enalapril Captopril Qinopril	Amlodipine Isradipine Nifedipine Verapamil h/chl.	Bendazole*

THE INTERVAL OF THE THERAPEUTIC AND TOXIC ACTION, LETHAL DOSES

Medicine	Int-l of the therap. action	Int-l of the toxic action	Lethal doses
Clonidine hydrochloride	0.2-2.0 mg	0.4-11.25 mg	> 0.1 mg/kg of body weight
Reserpine		5-260 mg	

SYMPATHOLYTICS

TOXICODYNAMIC OF RESERPINE

- Neurotoxicity: CNS depression, drowsiness, tremor
- Dermatotoxicity: redness of face and body, redness and edema of the mouth and pharynx
- Pulmotoxicity: edema of the mucous membranes of the nose, difficulty in nasal breathing
- Ophtalmotoxicity: Miosis with the reaction of pupils to light
- Gastrotoxicity: nausea, vomiting, persistent hiccups
- Cardiotoxicity: bradycardia, hypotension

THE MECHANISM OF TOXICITY OF RESERPINE

Reserpine irreversibly blocks the accumulation of catecholamines and serotonin in the granules of the nerve endings, chromaffin cells and bodies of neurons, it leads to decrease of biogenic amines in the CNS, and partly in the periphery. The tone of the sympathetic nervous system decreases and parasympathetic one rises: miosis, difficulty breathing, bradycardia

FACTORS ASSISTING TOXICITY OF RESERPINE

Reserpine potentiates the effect of hypnotics, anesthetics, muscle relaxants, adrenergic and cholinomimetic medicines, the hypotensive effect and bradycardia of β-blockers. Therefore, we must carefully prescribe the combination of Reserpine with Propranolol, etc. It increases cardiotoxicity of digitalis medicines.

FACTORS THAT DECREASE THE TOXIC EFFECT OF RESERPINE

Nasal obstruction as a complication while taking Reserpine can be eliminated by using Sanorin, Naphtisine. For prevention of intoxication of Reserpine it should be used in small doses, in combination with peripheral vasodilators (Hydralazine), myotropic spasmolytics (Bendazol), α-adrenoblockers (Prazosin), saluretics (Clopamid).

ANTIDOTES AND ANTAGONISTS

Reserpine antagonists are MAO inhibitors, restoring the balance of catecholamines and serotonin in the brain tissues.

PERIPHERAL VASODILATING MEDICINES

TOXICODYNAMICS

Medicines	Symptoms of overdoses				
	CVS	Kidney	CNS	GIT	Other
Sodium nitroprusside	Orthostatic hypotension	Metabolic acidosis			
Diazoxide		Hyperuricemia	Extrapyramidal reactions	Constipation	Hyperglycemia
Hydralasine h/chl.	Orthostatic hypotension, myocardial pain, tachycardia	Anuria	Dizziness, headache, fainting	Nausea, vomiting	Hyperthermia, allergic reaction (edema of the joints, rash)

THE MECHANISM OF TOXICITY OF PERIPHERAL VASODILATORS

Toxicity of sodium nitroprusside is associated with its metabolism and formation of cyanide, when the concentration of the latter in the blood plasma is above 120 mg/l it is considered to be toxic.

Headache, weakness, dizziness, loss of consciousness are because of redistribution of the blood: due to the intensive decrease of the vascular tone of the systemic blood flow, the blood flow in internal organs increases (kidneys, lungs, heart), there is decrease of IOP at the same time, sometimes leading to the loss of consciousness and fainting.

"Lupus syndrome" caused by disorders of cellular immunity and formation of IgG-containing complexes (formation of antinuclear antibodies), observed at doses above 200 mg/day

The phenomenon of the late intoxication: anemia, leukopenia, paresthesia and polyneuritis are developed by deficiency of vitamin $B_{6.}$

WHAT TO DO?

- Gastric irrigation with a suspension of activated charcoal and then intake of a saline laxative;
- During the orthostatic collapse: the introduction of Phenylephrine, Ephedrine, Caffeine-sodium benzoate subcutaneously
- Allergic reactions - prescription of antihistamines, glucocorticoids (GC).

SPASMOLYTICS
TOXICODYNAMICS OF BENDAZOL

***From the CVS**: collapse, tachycardia;*
***From the CNS:** dizziness, loss of consciousness*

WHAT TO DO?

- ❑ Gastric irrigation with a suspension of activated charcoal and then intake of a saline laxative
- ❑ Blood flow failure - analeptics (Camphor, Caffeine, Sodium benzoate, Cordiamin)

ACE INHIBITORS
TOXICODYNAMICS

- ❑ Hypotension
- ❑ Bradycardia
- ❑ Cardiovascular shock
- ❑ Electrolyte derangement
- ❑ Hyperkalemia renal failure

THE MECHANISM OF TOXICITY OF ACE INHIBITORS

Increase of concentrations of urea nitrogen and creatinine in serum is associated with intake by patients (in combination with ACE inhibitors) diuretic medicines, the nephrotic syndrome develops in the presence of proteinuria.

The renal dysfunction occurs in patients with a great water and sodium losses (intake of diuretics) or patients with renal artery stenosis. Blocking of the renin-angiotensin system in these patients with ACE inhibitors leads to an acute decrease of pressure in the glomeruli and the development of renal failure.

FACTORS ASSISTING TOXICITY OF ACE INHIBITORS

Patients with renovascular hypertension should use the ACE inhibitors carefully because of the risk of nephrotoxicity.

The combination of ACE inhibitors with potassium-sparing diuretics leads to hyperkalemia, and with loop and thiazide diuretics, β-adrenoblockers and other antihypertensives medicines, antipsychotics (phenothiazines) increases the hypotensive effect of nitrates, can cause collapse.

WHAT TO DO?

Symptoms	**Therapy**
Gastric irrigation, the adsorbing substance, solution of Sodium sulphate	
Hypotension	Completion of BCC by the i/v infusion of the physiological solution, i/v injections of catecholamines, ECG and the blood pressure control
Bradycardia	Solution of Atropin sulphate, an artificial pacemaker is implanted
Tissue edema involving the larynx, pharynx, tongue	Epinephrine in the dose of 0.3-0.5 mg, GC, anti-histamine medicines

ANTIARRHYTHMIC MEDICINES

Antiarrhythmics are medicines that normalize the rate and contractions of the heart preventing or removing arrhythmias.

CLASSIFICATION OF MEDICINES

Medicines removing					
tachyarrhythmia				**bradyarrhythmia**	
Membrane-stabilizers	β-adreno-blockers	Prolongers of repolari-zation	Calcium ca-nals blo-ckers, K+-containing medicines*	M-cholino-blockers	β-adren o-mi-metics
Quinidine Procainamide Lidocaine Moracizin Disopyramide Propafenon	Propranolol Metoprolol Sotalol Acebutolol Nadolol	Amioda-rone	Verapamil	Atropine sulphate	Iso-pre-naline

THE INTERVAL OF THE THERAPEUTIC AND TOXIC ACTION, LETHAL DOSES

Medicine	**Int-l of the therap. action**	**Int-l of the toxic action**	**Lethal doses**
Quinidine		2,5-4,0	
Disopyramide		2,5	49 mcg/ml
Moracizin	600-900 mg		2250 and 10000 mg
Praymalin	150-400 mg	850-2500 mg	
Lidocaine			6-53 mcg/ml
Propafenon		2200 мг- 4500 mg	4800 mg
Procainamide	10-37 mcg/ml		

TOXICODYNAMICS OF QUINIDINE

- Cardiotoxicity: atrioventricular blockade, asystole, suppression of the myocar-dial contractility, heart failure, decrease of TPVR and myo-cardial depression, pulmonary edema
- Gastrotoxicity: abdominal pain, diarrhea
- Hematotoxicity: thrombocytopenia, hemoly-tic anemia

- ❑ Hepatotoxicity: cholestatic hepatitis
- ❑ Allergic reactions: drug fever, systemic lupus erythematosis, anaphylaxis

«Cinchonism» - drug intoxication by alkaloids of Cinchona (Quinidine)

Sever cinchonism is accompanied with coma, convulsions, heart and breath stoppage, hypotension

Acute intoxications	Chronic intoxications
Headache, fever, mydriasis, visual disorders, hearing loss, organic brain damage (memory loss, delirium, nau-sea, vomiting, rash, flushing skin with the tides)	Chronic brain injury, *** quinine amblyopia is the loss of vision (complete and sudden) strongly dilated and non-reactive pupils ***

*** - the main symptom of intoxication by Quinidine

THE MECHANISM OF TOXICODYNAMIC OF QUINIDINE

- ❑ Vision disorders is the result of the cholynolitic effect.
- ❑ Hypotension is the result of its α - adrenolytics activity: myocardial depression and decrease of the vascular tone.

WHAT TO DO?

Antidotes **– Glucagon, Bretilium**

Symptoms	Therapy
Acute heart failure	the introduction of oxygen, i/v infusions
Convulsions	Diazepam
Purification and detoxication of gastro-intestinal tract	Induced vomiting and gastric lavage, activated charcoal, laxative medicines
Hypotension	Infusion therapy, vasoconstrictors: Isoproterenol, Norepinephrine
Ventricular arrhythmias	Lidocaine, Phenytoin, Isoproterenol

FACTORS ASSISTING TOXICITY OF QUINIDINE

- ❑ Combination of Quinidine and Propranolol increase the negative chronotropic effect of both medicicnes and the Quinidine intoxication increases
- ❑ Diuretics that cause hypokalemia, Rifampicin, antiepileptic medicines (Phenobarbital, Phenytoin, Primidone), Cimetidine, Fluconazole, Ketoconazole increase the toxicity of Quinidine.
- ❑ Calcium-magnesium-containing antacids, Sodium citrate, Sodium bicarbonate increase the cardiotoxicity of Quinidine

TOXICODYNAMIC OF PRAYMALIN

- Cardiotoxicity: the 1st stage of atrioventricular blockade, arrhythmogenic effect, heart stoppage
- Neurotoxicity: generalized clonic convulses, ataxia, epileptic states, unconsciousness, apnea
- Gastrotoksichnost: nausea, vomiting

THE MECHANISM OF TOXICODYNAMIC OF PRAYMALIN

The arrhythmogenic effect is the result of blockade of impulse conduction and the possibility of atrial extra systole to induce a circular wave of excitation and arrhythmogenic sites (such as "pirouette") appearance due to early post depolarization.

WHAT TO DO?

Symptoms	Therapy
Heart failure, arrhythmia	Oxygenation, i/v infusion
Gastrointestinal symptoms	Before the gastric lavage a pacemaker should be installed i/v to avoid the irritation of the vagus nerve and increase bradycardia
Epileptic state	Methoraminol

TOXICODYNAMIC OF LIDOCAINE

- Cardiotoxicity: inhibition of myocardial contractility, respiratory distress syndrome in adults, hypotension, decrease in the heart rate, tremor and lack of response to stimulation, coma, respiratory stoppage
- Hematotoxicity: acute methaemoglobinemia
- Neurotoxicity: dizziness, confusion, ataxia, hearing loss, euphoria
- Visual disorders are evidence of toxic concentrations of Lidocaine

WHAT TO DO?

Symptoms	Therapy
Cardiotoxicity	Dopamine, Epinephrine, Atropine, intubation
Convulsions	Diazepam
Hypoxia	Provide gas exchange and the acid-base balance

TOXICODYNAMICS OF PROCAINAMIDE

- Cardiotoxicity: prearrhythmic effect "piruet cardiac arrhythmia", ventricular tachycardia, ventricular fibrillation, hypotension, shock
- Neurotoxicity: paresthesia, drowsiness, weakness, dizziness, "dreams as reality"
- Gastrotoxicity: nausea, vomiting, diarrhea, anorexia

- Other toxic reactions: vision disorders, skin rashes

THE MECHANISM OF TOXICODYNAMIC OF PROCAINAMIDE

The mechanism of the arrhythmogenic effect of procainamide is associated with a blockade of impulse conduction and the possibility of atrial extrasystole to induce a circular wave of excitation, prolonging QT and arrhythmogenic sites (such as "pirouette") appearance due to early post depolarization.

WHAT TO DO?

Intravenous infusion of oxygen, cardiac monitoring, hemoperfusion, the introduction of adrenergic agonists such as Dopamine, Phenylephrine, Norepinephrine

PRACTICE ON TOXICOLOGY

TOPIC OF THE LESSON 1:

GENERAL TOXICOLOGY

Theoretical issues:

1. Give the definition and the aim of toxicology.
2. Give the definition of toxicity.
3. Describe the types of toxicants.
4. Describe the structure of toxicology.
5. Give the definition of toxicodynamics.
6. Give the definition of toxicokinetics.
7. Give the definition and classification for antidotes.
8. Kinds, periods of intoxication.

In-class tasks:

Task 1

Fill in the table, use the information from the lecture

Antidotes	**Type of antagonism**	**Toxicants**
	Chemical	
	Biochemical	
	Physiological	
	Modification of metabolism	

Task 2

Fill in the table, use the information from the lecture

Medicines	**Expected effect**	**Examples**
Etiotropic		
Pathogenic		
Symptomatic		

Task 3

Rewrite the table and discuss it with a teacher

Class of toxicity	**Enteral route of administration (LD50 mg/kg)**	**Inhalation route (LD50 mg/kg)**	**Limit concentration mg/m3**
Highly toxic	< 15	< 1	< 1
Very toxic	15-150	1-10	10
Toxic	151-1500	11-40	100
Low toxic	>1500	> 40	> 100

TOPIC OF THE LESSON 2:

TOXICOLOGY OF MEDICINES AFFECTING THE CENTRAL NERVOUS SYSTEM (CNS)

Theoretical issues:

1. Classification of the medicines that depress the CNS.
2. Classification of the medicines that stimulate the CNS.
3. The range of therapeutic and toxic doses of the medicines that stimulate the CNS. Potentially toxic medicines in each group.
4. The basic mechanisms of drug toxicity of antipsychotics, tranquilizers, sedatives, hypnotics, anticonvulsants, antiparkinsonian medicines.
5. The basic mechanisms of drug toxicity of analeptics, psychostimulants, antidepressants.
6. Toxicodynamics of the medicines affecting the CNS.
7. Peculiarities of medicines toxicokinetics.
8. Treatment of intoxication caused by the medicines affecting the CNS.
9. Prevention of intoxication caused by the medicines affecting the CNS.

In-class tasks:

Task 1

You need to combine the mechanism of antipsychotic toxic action with the toxic effects. Match numbers and letters.

Mechanism of toxic action	Toxic effects
1.Blockade of H_1- histamine receptors	a. Dry mouth
2. M-cholinolytic activity	b. Hypotension
3.α1-adrenoblocking activity	c. Neuroleptic syndrome
4. Blockade of dopamine receptors	d. Sedative, hypnotic effect

Task 2

To prepare the information about the toxic effects of antipsychotic medicines, fill in the table using «+» if the effect is present and «–» if it is absent.

Medicines	Toxic effects					
	NS*	Cardiotox-icity	Orthostatic hypoten-sion	Dry mouth	Convul-sions	↓ Hemo-poiesis
Chlorpromazine						
Droperidol						
Clozapine						

*Neuroleptic syndrome (NS)

Task 3

From the proposed list of toxic effects choose the correct ones for Chlorpromazine (A), Diazepam (B). Match numbers and letters.

1. Dry mouth
2. Neuroleptic syndrome
3. Convulsions
4. Tachycardia
5. Disorders of diuresis
6. Decrease of skeletal muscles tone
7. Drowsiness, weakness, depression
8. Worsening of attention and locomotion

Task 4

Name the antidote that will be used in cases of poisoning by Diazepam (A), Barbiturates derivatives (B):

1. Codeine
2. Atropine sulphate
3. Dipiroxim
4. Bemegride
5. Paracetamol
6. Naloxone
7. Unithiol
8. Neostigmine methylsulphate
9. Calcium chloride

Task 5

You need to choose the toxic effects of Phenobarbital (A), and Sodium bromide (B):

1. Tachycardia, hypertension
2. Mydriasis
3. Heart stoppage
4. Acute liver and renal disfunction

5. Nephrotoxicity, hematotoxicity
6. Sedation, lacrimation
7. Convulsions, excitation.

Task 6

To prepare the information of the anticonvulsants toxic effects, fill in the table. Use «+» to note the presence of effect, use «–» to note it is absent.

Medicines	Toxic effects					
	Atrioventricular blockade	Megaloblastic anemia	Convulsions	Alopecia	↓BP	depression of respiration
Valproic acid						
Diphenin						
Carbamazepine						
Clonazepam						
Phenobarbital						

Task 7

You need to choose the toxic effects after poisoning by bromides:

1. Mercurism
2. Bromism
3. Iodism
4. Mydriasis
5. Hyperglycemia.

Task 8

Prepare the information about the toxic effects of antipsychotics, tranquilizers, sedatives, hypnotics, anticonvulsants, antiparkinsonians, fill in the table using «+» if the effect is present and «–» if it is absent.

Medicines symptoms	**Diphenin**	**Diazepam**	**Levodopa**	**Droperidol**	**Nitrazepam**
Euphoria					
Insomnia					
Psychosis					
Sleepiness					
Disorder of the hormonal metabolism					

Neuroleptic syndrome					
Convulsions					
Hypotension					
Tachycardia					
Withdrawal syndrome					
Intestine atonia					
Mydriasis					
Hypotermia					
Pain in the epigastrium					
Nausea, vomiting					

Task 9

Prepare the information about toxic effects of the CNS stimulants, fill in the table. Use «+» to note the presence of effect, use «–» to note its absence.

Symptoms	**Amphethamine sulphate**	**Caffeine**	**Amitriptyline**	**Nialamide**	**Strychnine**
Euphoria					
Insomnia					
Sleepiness					
Brain edema					
Convulsions					
↑BP					
Tachycardia					
Myocardial infarction					
Dysfunction of heart conductivity					
Anorexia					
Nausea, vomiting					
Pain in the					

epigastrium					
Atonia of intestine					
Polyuria					
Mydriasis					
Hypotermia					
Metabolic acidosis					
Dryness of the skin					

Task 10

Describe the symptoms of poisoning by Amphethamine sulphate and Caffeine. Fill in the table using «+» if the effect is present and «–» if it is absent.

Symptoms	**Amphethamine sulphate**	**Caffeine**
Psychic dependence		
Depression		
Psychosis		
Insomnia		
Sexual dysfunctions		
Anorexia		
Immune depression		
Tachycardia		
Anxiety, irritability, conflict behavior		

Task 11

Analyze of «STEP-2» quetion. Medicines: Sodium valproate, Nitrazepam, Levo-dopa, Chlorpromazine (Aminazine), Diazepam, Droperidol, Caffeine.

Control of the knowledge acquired (Tests)

1. Choose the antidote for treating intoxication by benzodiazepines:
A. Naloxone
B. Flumazenil
C. Atropine
D. Dipiroxim
E. Acetylcystein.

2. Choose the toxic effects of Strychnine:
A. Hypotension, bradycardia
B. Edema, bleedings
C. Hemato-, hepatotoxicity
D. Hypersalivation, myosis
E. Respiratory stoppage, strong convulsions.

3. Choose the toxic effects of Nialamide:
A. Anxiety, hypotension, dry mouth
B. Hypersalivation, myosis
C. Myosis, noise in the ears
D. Hemato-, hepatotoxicity
E. Edema, bleedings.

4. Choose the toxic effects of Caffeine:
A. Heart stoppage, convulsions
B. Hypotension, bradyarrhythmia
C. Excitement, hypertension, convulsions
D. Edema, nausea
E. Hypotension, inhibition of respiration.

5. Choose the toxic effects of tranquilizers:
A. Tachyarrhythmia, respiratory stoppage
B. Hypertension, pulmonary edema
C. Myosis, strong headache
D. Mydriasis, noise in the ears
E. Sleepiness, inhibition of the CNS.

6. Choose the toxic effects of Valproic acid:
A. Constipation, urinary reteention
B. Hypotension, nausea, convulsions, alopecia
C. Tachyarrhythmia, hypertension
D. Acute renal failure, constipation
E. Mydriasis, excitement.

7. Choose the toxic effects of Sodium bromide.
A. Hypertension, tachycardia
B. Nephro-, hematotoxicity
C. Sleepiness, lacrimation
D. Hepato-, ototoxicity
E. Excitement, convulsions.

8. Choose the toxic effects of analeptics.
A. Hypertension, tachyarrhythmia, convulsions
B. Bradycardia, hypotension
C. Myosis, noise in the ears
D. Nephro-, ototoxicity
E. Spasm of the intestine and bladder.

9. Choose the toxic effects of Phenobarbital.
A. Tachycardia, hypertension
B. Mydriasis, noise in ears
C. Inhibition of consciousness, respiration
D. Acute hepatic and renal failure

E. Myosis, severe headache.

10. Choose the antidote for treating intoxication by Diazepam.
A. Flumazenyl
B. Atropine
C. Naloxone
D. Paracetamol
E. Neostigmine.

11. Choose the toxic effects of Nitrazepam.
A. Mydriasis, dry mouth
B. Hypertension, tachycardia
C. Inhibition of the CNS, sleepiness
D. Excitement, convulsions
E. Hemato-, nephrotoxicity.

12. Choose the toxic effects of Diazepam.
A. Mydriasis, dry mouth
B. Hypertension, tachycardia
C. Inhibition of the CNS, sleepiness
D. Excitement, convulsions
E. Hemato-, nephrotoxicity.

13. Choose the toxic effects of Amphetamine.
A. Psyhosis, insomnia, tachycardia
B. Hypotension, bradycardia
C. Sleepiness, the CNS inhibition
D. Myosis, noise in the ears
E. Edema, hemorrhage.

14. Choose the toxic effects of Amitryptillin.
A. Atonia of the intestine and bladder
B. Mydriasis, dry mouth, sleepiness
C. Excitement, hypertension
D. Tachycardia, fever
E. Inhibition of respiration, myosis.

15. Choose the medicine for treating intoxication by analeptics.
A. Naloxone
B. Flumazenil
C. Diazepam
D. Neostigmine
E. Bemegride.

16. Choose the medicines for treating intoxication by Caffeine.
A. Narcotic analgesics
B. Analeptics
C. Cholinoblockers

D. Antidiarrheal medicines
E. Sedatives.

17. Choose the medicines for treating intoxication by Amphethamine sulphate:
A. Hypotensive, anti-arrhythmic, sedative medicines
B. Cholinoblockers, NSAIDs
C. NSAIDs, analeptics, diuretics
D. Diuretics, antibiotics, hemostatics
E. Antidepressant, local anaesthetic, anti-anginal medicines.

18. Choose the medicine for treating intoxication by Strychnine.
A. Naloxone
B. Flumazenil
C. Diazepam
D. Neostigmine
E. Bemegride.

19. Choose the toxic effects of Sodium diclofenac:
A. Weakness, hypotension
B. Mydriasis, frequent urinations
C. Headache, bleedings, abdominal pain
D. Methemoglobinemia, renal failure
E. Heart stoppage, convulsions.

20. Choose the toxic effects of Clonidine:
A. Weakness, hypotension, cardiogenic shock
B. Hypersalivation, intestinal spasm
C. Mydriasis, frequent urinations
D. Myosis, inhibition of respiration
E. Neuro-, cardiotoxicity.

TOPIC OF THE LESSON 3:

TOXICOLOGY OF OPIOID ANALGESICS, NON-OPIOID ANALGESICS, NSAIDs

Theoretical issues.

1. Classification of the opioid analgesics.
2. Classification of the non-opioid analgesics.
3. Classification of NSAIDs.
4. The range of therapeutic and toxic doses of pain pharmacocorrectors. Potentially toxic medicines are in each group.
5. The basic mechanisms of toxic effects of pain pharmaocorrectors.
6. Toxicodynamics of the pain pharmacocorrectors.
7. Peculiarities of toxicokinetics of these medicines.
8. Treatment of intoxication caused by the pain pharmacocorrectors.
9. Prevention of intoxication caused by the pain pharmacocorrectors.

In-class tasks:

Task 1

To prepare the information about the toxic effects of analgesics and opioid analgesics, fill in the table. Use «+» to note the presence of effect, use «–» to note its absence.

Medicines	Toxic effects			
	Inhibition of respiratory centre	Bradycardia	Myosis	Bronchospasm
Morphine				
Omnopone				
Trimeperidine				
Codeine				
Phentanyl				

Task 2

From the proposed list of toxic effects choose the correct ones for Paracetamol (A) and Sodium methamizol (Analgine) (B). To do it, combine the indexes of numbers with the letter (A) and (B).

1. Methehemoglobinemia
2. Dysfunctions of the GIT
3. Cyanosis of the mucous membranes
4. Weakness, dizziness
5. Stomach bleeding
6. Convulsions

Task 3

Choose the main symptoms of poisoning by NSAIDs (non-steroidal anti-inflammatory drugs)

1. Toxic gastroenteritis
2. Hematuria
3. Pulmonary edema
4. Dehydration of the body

Task 4

Choose what helps in case of poisoning by Acetylsalicylic acid (ASA):

1. Stomach washing
2. Stopping of allergic reaction
3. Stopping of bleedings
4. Alkaline urine

Explain your answer.

Task 5

Name the antidote for Morphine (A) and Paracetamol (B).

1. Bemegride
2. Caffeine sodium benzoate
3. Diazepam
4. Naloxone
5. Phenobarbital
6. Acetylcystein

Task 6

Choose the symptoms of poisoning by Opioid analgesics.

1. Tachycardia
2. Bradycardia
3. Hypertension
4. Myosis
5. Hypotermia
6. Hypertermia
7. Liver cirrhosis
8. Periodic breathing

Task 7

Choose correct symptomatic therapy for treatment of poisonings by Opioid analgesics (A), Paracetamol (B), ASA (C):

1. Stomach washing by Potassium permanganate
2. Salt laxative
3. High doses of Ascorbic acid
4. Plenty of weak alkaline drink decreasing the acidity of urine.
5. Activated charcoal

Task 8

Choose the symptoms of poisoning by ASA.

1. Tachycardia
2. Bradycardia
3. Hypertension
4. Bleeding diarrhea
5. Hypotermia
6. Hypertermia
7. Bluster in the ears
8. Periodic breathing
9. Hemorrhages on the skin

Task 9

Analyze the «STEP-2» questions. Such medicines as: Morphine, Trimeperidine, Naloxone, Paracetamol, Sodium diclofenac, Acetylsalicylic acid.

Control of the knowledge acquired (Tests)

1. Choose the main symptoms of poisoning by Morphine.
A. Myosis, headache
B. Myosis, periodic breathing
C. Mydriasis, bluster in the ears
D. Mydriasis, tachycardia
E. Acute renal and liver dysfunctions

2. What medicine shoud be used in case of opioid analgesic overdose as an antidote to stop the respiratory centre depression?
A. Etymisol
B. Nicethamide
C. Naloxone
D. Camphor
E. Paracetamol.

3. A woman of 25 was injected naloxone to prevent an acute morphine intoxication. Naloxone improved her condition rapidly. What is the mechanism of action of this medicine?
A. Block of opioid receptors
B. Block of GABA receptors
C. Block of serotonin receptors
D. Block of dopamine receptors
E. Block of benzodiazepine receptors.

4. Choose the main symptoms of poisoning by Sodium methamizole
A. Myosis, headache
B. Bleedings, hypotension, hepatitis

C. Mydriasis, tachycardia
D. Spasm of the intestine, bladder
E. Acute pulmonary edema.

5. Explain to your colleague-pharmacist, what indications naloxone has?
A. Heavy metal poisoning
B. Acute narcotic analgesic poisoning
C. Cardiac glycosides poisoning
D. Ergot alkaloid poisoning
E. Atropine sulphate poisoning.

6. A patient in the comatose state was hospitalized to the emergency department. He has such symptoms as hypotension, bradycardia, hypothermia, anuria (absence of urination), and periodic breathing. His diagnosis was poisoning with Morphine. The doctor recommended to take the antagonist of Morphine for antidote therapy. What is this antagonist?
A. Lobeline
B. Pentazocine
C. Nalorphine hyrochloride
D. Cordiamine (Nicethamide)
E. Naloxone.

7. Choose the main symptoms of poisoning by Acetylsalicylic acid
A. Asphixia, bradycardia
B. Hemorrhages, bluster in the ears, bleeding diarrhea
C. Mydriasis, hypersalivation
D. Constipation, anuria
E. Acute liver disfunction and methemoglobinemia.

8. Name the antidotes for Morphine (1) and Paracetamol (2).
A. Bemegride
B. Phenobarbital
C. Diazepam
D. Naloxone
E. Acetylcystein
F. Caffeine-sodium benzoate.

9. Choose correct symptomatic therapy in cases of poisoning by Opioid analgesics:
A. Stomach washing by Potassium permanganate
B. Intake of salt laxatives
C. Injections of Glucose
D. Plenty of weak alkaline drink decreasing the acidity of urine
E. Use of emetic medicines

TOPIC OF THE LESSON 4:

TOXICOLOGY OF MEDICINES AFFECTING EFFERENT INNERVATION

Theoretical issues:

1. Classification of the medicines affecting the efferent part of the nervous system
2. The range of therapeutic and toxic doses of the medicines affecting the efferent part of the nervous system. Potentially toxic medicines are in each group.
3. The basic mechanisms of toxic action of drugs affecting the efferent part of the nervous system.
4. Toxicodynamics of the medicines affecting the efferent part of the nervous system..
5. Peculiarities of medicines toxicokinetics.
6. Treatment of intoxication caused by the medicines affecting the efferent part of the nervous system.
7. Prevention of intoxication caused by the drugs affecting the efferent part of the nervous system

In-class tasks:

Task 1

Prepare the information about toxic effects of anticholinesterase medicines. Fill in the table using «+» if the effect is present and «–» if it is absent.

Medicines	Toxic effects					
	Broncho-spasm	Bradycardia	Myosis	Dry mouth	Con-vul-sions	↑ blood pressure
Anticholinesterase medicines						

Task 2

From the proposed list of toxic effects choose the correct ones for Atropine sulphate (A). Match letter and numbers.

1. Myosis
2. Dry mouth
3. Psychosis
4. Tachycardia
5. Stomach bleeding
6. Mydriasis
7. Disorders of diuresis
8. Accommodation paralysis.

Task 3

Name the antidote that is used in poisoning by Neostigmine (Proserine):

A. Codeine B. Morphine C. Dipiroxim D. Bemegride E. Paracetamol.

Task 4

Choose the most toxic medicines from the following list using the information from the theoretical issues 2.

1. Cholinomimetics
2. Anticholinesterases
3. M-Cholinoblockers
4. Ganglionic blockers
5. Muscle relaxants
6. Adrenomimetics
7. Adrenoblockers.

Task 5

Choose a medicine that is used in case of poisoning by Atropine sulphate (A):

A. Calcium chloride B. Magnesium sulphate C. Neostigmine D. Epinephrine E. Trimeperidine

Task 6

Prepare the information about the toxic effects of adrenomimetics, fill in the table. Use «+» to note the presence of effect, use «–» to note its absence.

Medicines	Toxic effects					
	Arrhythmia: - bradyarrhythmia - tachyarrhythmia	Bronchospasm	Hyperglycemia	CNS stimulation	↑BP	Breathing of Chein-Stocs type
Adrenomimetics						

Task 7

From the proposed list of toxic effects select those that characterize β-Adrenoblockers (B). To do it combine the indexes of numbers with the letter (B).

1. Heart stoppage
2. Tachycardia
3. Bronchospasm
4. Increase BP
5. Collapse
6. CNS depression
7. Increase of sweating.

Task 8

Analysis of «STEP-2». Medicines: Atropine sulphate, Pilocarpine, Neostigmine methylsulphate, Dithylinum, Epinephrine (Adrenaline hydrochloride), Salbutamol, Propranolol (Anaprilin), Metoprolol.

Control of the knowledge acquired (Tests)

Variant № 1

1. A child with signs of poisoning by Belladonna alkaloids was delivered to the hospital. Name the antidote that should be administered.
A. Tubocurarine
B. Magnesium sulfate
C. Sodium valproate
D. Neostigmine
E. Caffeinesodium benzoate.

2. A dentist hasa need to reduce salivation during the surgery. What pharmacological group of medicines will he use?
A. M-cholinomimetics
B. M-cholinoblockers
C. Adrenomimetics
D. Adrenoblockers
E. N-Cholinomimetics.

3. A patient with hypertensive crisis was injected ganglionic blocker – Benzohexonium. What side effect can appear after the injection?
A. Disorders of taste sensations
B. Diarrhea
C. The withdrawal syndrome
D. Orthostatic hypotension
E. The CNS depression.

4. To increase blood pressure of a patient the medicine affecting the efferent part of the nervous system was taken. Intramuscular injection of this medicine caused necrosis of tissue. What medicine was administred by the patient?
A. Mesatone phenylephrine
B. Norepinephrine
C. Epinephrine
D. Salbutamol
E. Ephedrine

5. During the treatment of arrhythmia non-selective β-Adrenoblocker was used. What is this medicines?
A. Enalapril
B. Propranolol
C. Epinephrine
D. Neostigmine
E. Atropine.

Control of the knowledge acquired (Tests)

Variant № 2

1. The patient of 70 years old has increased blood pressure and concomitant the prostate adenoma. What medicine should be prescribed in this case?
A. Losartan
B. Doxazosin
C. Propranolol
D. Dilthiazem
E. Enalapril.

2. Answer the patients' question, what medicine is contraindicated in case of hypertension combined with bronchial asthma.
A. Prazosin
B. Propranolol
C. Drotaverine
D. Magnesium sulphate
E. Lisinopril.

3. After bee stings angio-neurotic edema has been developed in the patient. What medicine should be prescribed?
A. Atropine
B. Sodium chloride
C. Platiphylline
D. Epinephrine
E. Propranolol (Anaprilin).

4. A child has symptoms of poisoning by Belladonna alkaloids. Name the antidote that should be administered.
A. Paracetamol
B. Sodium valproate
C. Caffeine
D. Magnesium sulphate
E. Neostigmine.

5. What is the most characteristic symptom of poisoning by Atropine?
A. Decrease of intraocular pressure
B. Increased sweating
C. Bradycardia
D. Myosis and presense of reaction to light
E. Mydriasis and absence of reaction to light.

TOPIC OF THE LESSON 5:
TOXICOLOGY OF MEDICINES AFFECTING THE CARDIOVASCULAR SYSTEM

Theoretical issues:

1. Classification of the medicines affecting the cardiovascular system
2. The range of therapeutic and toxic doses of the medicines affecting the cardiovascular system. Potentially toxic medicines are in each group.
3. The basic mechanisms of the toxic action of drugs affecting the cardiovascular system.
4. Toxicodynamics of the medicines affecting the cardiovascular system.
5. Peculiarities of drug toxicokinetics.
6. Treatment of intoxication caused by the medicines affecting the cardiovascular system.
7. Prevention of intoxication caused by the drugs affecting the cardiovascular system.

In-class tasks:

Task 1

To prepare the information about cardiac glycosides toxic effects, fill in the table using «+» if the effect is present and «–» if it is absent.

Medicines	Toxic effects					
	Disorders of vision	Bradycardia	Mydriasis	Bronchospasm	Hypokalemia	Hallucination
Cardiac glycosides						

Task 2

Point out the antidote that is used in poisoning by cardiac glycosides:
A. Naloxone B. Atropine C. Dipiroxim D. Bemegride E. Unithiol.

Task 3

To prepare the information about toxic effects of nitrovasodilators, fill in the table. Use «+» to note the presence of effect, use «–» to note its absence.

Medicines	Toxic effects					
	Strong headache	Methaemoglobinemia	Mydriasis	Cyanosis	Inhibition of the respiratory centre	Hallucination
Nitrovasodilators						

Task 4

Point out the lethal dose of Glycerol trinitrate.
A. 5.0 B. 2.0 C.1.0 D. 10.0

Task 5

What medicines are antagonists of the toxic effects of cardiac glycosides?

A. Calcium-containing medicines
B. Potassium-containing medicines
C. magnesium-containing medicines
D. silver-containing medicines

Task 6

To prepar the information about ACE inhibitors toxic effects, fill in the table. Use «+» to note the presence of effect, use «–» to note its absence.

Medicines	Toxic effects					
	Angioneu-rotic ede-ma	Tachyar-rhythmia	Hypo-tensive	Hyper-tensive	Hyper-kalemia	Hypo-kalemia
Lisinopril						

Task 7

Choose the type of cardiotoxicity of Lidocain:

A. The negative chronotropic and dromotropic effects
B. Piruetic altering of the heart rhythm
C. Slowdown of the sinus rhythm
D. Atrioventricular blockade

Task 8

Name the antidote that is used in case of poisoning by Qunidine:

A. Atropine B. Glucagone C. Dipiroxim D. Bemegride E. Deferoxamine.

Task 9

What medicine is used for prevention hypokalemia caused by cardiac glycosides?

A. Panangine B. Amiodarone C. Unithiol D. Bemegride E. Deferoxamine.

Task 10

The mechanism of the toxic effect of cardiac glycosides is connected with inhibition of such enzyme as:

A Na^+-K^+-ATPase B Alcoholdehydrogenase C Succinate-dehydrogenase.

Task 11

Choose the medicine used for treatment of arrhythmias caused by cardiac glycosides intoxication:

A. Atropine B. Lidocaine C. Dobutamine D. Phenitoin.

Task 12

Analysis of «STEP-2». Medicines: Digoxin, Corglycon, Nitroglycerine, Isosorbide mononitrate, Amiodaron, Lisinopril, Enalapril, Hydrochlorthiazide, Furosemide.

Control of the knowledge acquired (Tests)

1. What medicines are necessary for treatment of arrhythmias caused by β-adrenoblockers:
A. Hypotensives
B. Anticonvulsants
C. Anti-anginals
D. Anti-arrhythmics
E. Hypoglycemics.

2. What medicine may be used for treatment of hypotension caused by overdose of α_1-adrenoblockers:
A. Levodopa
B. Atropine
C. Propranolol
D. Diazepam
E. Noradrenaline.

3. Choose the toxic effects of α-adrenoblockers.
A. Myosis, tachycardia
B. Hypotension, weakness
C. Mydriasis, frequent urinations
D. Hypertension, excitement
E. Hyperglycemia, absence of urination.

4. Choose the toxic effects of Clonidine.
A. Weakness, hypotension, cardiogenic shock
B. Hypersalivation, intestinal spasm
C. Mydriasis, frequent urination
D. Myosis, inhibition of respiration
E. Neuro-, cardiotoxicity.

Дане видання є конспектом лекцій та практичним посібником з тестовими завданнями з токсикології.

Користуючись конспектом лекцій, який має чітку та логічну структуру, майбутній спеціаліст зможе підготуватися до вирішення професіональних ситуацій, які знаходять своє інформаційне відображення у практичному посібнику з тестовими завданнями.

Дане видання рекомендоване для студентів фармацевтичних вузів та фармацевтичних факультетів вищих медичних закладів.

Навчальне видання

Дроговоз Світлана Мефодіївна
Куценко Тетяна Олександрівна
Позднякова Анастасія Юріївна
Уланова Віра Анатоліївна

ТОКСИКОЛОГІЯ

Конспект лекцій, практичний посібник з тестовими завданнями з токсикології

Англійською мовою