MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION VOLGOGRAD STATE MEDICAL UNIVERSITY DEPARTMENT OF PHARMACEUTICAL AND TOXICOLOGICAL CHEMISTRY

LECTURE 1

TOXICOLOGIKAL CHEMISTRY

Introduction to toxicological chemistry. The main sections of toxicological chemistry. Organization of chemical-toxicological expertise in the Russian Federation. Toxicokinetics. General patterns of distribution of poisons in the body. Factors of influence on the toxicity of xenobiotic.

Maria Petrovna Paramonova Assistant professor, PHD **Toxicological chemistry** is the science of chemical transformations of toxic substances and their metabolites in the body, methods for their isolation from objects of biological origin, detection and quantification.

Toxicological chemistry is special pharmaceutical discipline and is interconnected with other disciplines:

- medical (pharmacology, forensic and clinical toxicology);
- biological (biochemistry, biology, pharmacognosy);
- chemical (pharmaceutical, analytical, inorganic, organic, physical and other chemistry)

Sections of toxicological chemistry

Narcological-

Analytical diagnosis of drug addiction and substance abuse

Clinical -Analytical diagnosis of acute and chronic poisoning

Forensic chemicalidentifies causes poisoning based on material evidence

Eco-toxicological

• safety medicines

 professional toxicology(risk assessment of working with chemical substances), environmental toxicology(action of toxicants, contained in water, air and soil on biological objects).

Chemical-toxicological analysis (CTA) - scientifically based methods used to isolate, detect and quantifydetermination of toxic substances.

CTA Features:

- Variety of objects of study: biological fluids (blood, urine), vomit, internal organs of human corpses, hair, nails, food and drink residues, medicines, pesticides, clothes, water, soil etc.
- 2. The need to isolate (recover) small amounts (from mg to μg) search chemicals from a relatively large amount of the objectresearch.
- 3. Working with very small quantities of a substance mixed with related(co-extractive, ballast) substances extracted during isolation, and often have a negative impact on the results of the analysis. It is necessary to remove these ballast substances by introducing additional methods cleaning
- 4. use of sensitive and specific methods of analysis

Organizational structure of forensic medical and forensic chemical expertise in the Russian Federation

Ministry of Health of the Russian Federation

Russian Center for Forensic Medical Examination

- Bureau of Forensic Medical Examination of Republics, Regions and Cities
- Department of living persons
- department of corpses
- Department of material research evidence

The legal and methodological foundations of forensic chemical expertise are regulated by:

- Order of the Ministry of Health and Social Development of the Russian Federation No. 346 / n dated May 12, 2010 "On approval of the procedure for the organization and production of forensic medical expertise in state forensic institutions of the RussianFederations"
- 2. Order of the Ministry of Health and Social Development of the Russian Federation No. 40 dated January 27, 2006 "On organization of chemical and toxicological studies in analytical diagnosis of the presence of alcohol in the human body, narcotic drugs, psychotropic and other toxic substances

Objects of study

 When conducting a study on alcohol, narcotic and psychotropic substances in the **body of the living (40)**, take:
 blood from a vein (do not wipe with an alcohol antiseptic, add heparin)

- urine 30-100 ml (primary control is carried out to prevent falsification. pH, density, temperature, creatinine are determined)
- hair (from the head, if not, then from the pubis or from the armpits)
- nails (hands, feet)
- saliva
- sweat-fat washings from the skin

Objects of study:

- 2 When conducting a forensic expertise (dead) (346):
- non-directed study 1/3 liver, 1 kidney, stomach with contents, blood, urine, gallbladder and bile, 1 meter of the small intestine. !!!!
- 3. If you suspect the introduction of poison through the vagina or uterus additionally, the uterus and vagina are directed separately.
- 4. If subcutaneous or intramuscular injection is suspected the site skin or muscle from the injection site.

- 5. If inhalation is suspected ¼ of the lung, 1/3 of the headbrain.
- 6. contents of the stomach grains, crystals, tablets
- The same objects can be vomit, the first portions of washing stomach waters, residues of medicinal and chemical substances, food, drinks and other objects

In case of suspected poisoning, additionally send:

- 1. Acids, alkalis pharynx, trachea and esophagus, skin area with traces of action poison.
- Volatile organic substances (chloroform, carbon tetrachloride, dichloromethane, organochlorine pesticides and other alkyl halides) - stuffing box, 1/3brain
- 3. Methyl alcohol 1/3 of the brain.
- 4. Glycosides 1/3 of the liver with a gallbladder.
- 5. Phosphorus organic compounds necessarily blood (to determine the activitycholinesterase)
- 6. Mercury salts rectum, hair.
- 7. Chronic poisoning with lead compounds, waist flat bones.
- 8. Chronic poisoning with arsenic compounds hair, nails, flat bones.
- 9. Tetraethyl lead brain, lungs.

In case of suspected poisoning, additionally send:

- 10. Carbon monoxide blood, muscle tissue.
- Ethanol blood from large veins, urine, if not possible about
 g of musclefabrics.
- 12. Methemoglobin-forming poisons (aniline, nitrobenzene, potassium permanganate, formaldehyde, chromates, acetaldehyde) blood for methemoglobin.
- 13. Mushrooms and poisonous plants undigested pieces from the contents of the stomach, vomit, washings.

Tasks of forensic chemical expertise:

- determination of toxicologically important substances to establishcauses of death;
- identification of medicinal and narcotic substances that can affect a person's condition;
- qualitative and quantitative analysis of narcotic substances in biological material and other samples relevant to forensic and forensic practice;
- - obtaining analytical results, subsequent interpretation

Basic rules of forensic chemical analysis

- 1. The analysis must be started on the day the objects are received for analysis. If this is not possible, then the objects are stored in a refrigerator.
- 2. The expert carefully examines the objects and describes them in the workingmagazine. object must matchaccompanying document.
- 3. The expert carefully examines the documents and draws up a planresearch.
- 4. For analysis, 2/3 of the sent objects are spent, and 1/3 remains in the archive forre-analysis if necessary.
- 5. Research can be done on specific compound, group of substances or an unknown substance according to the schemegeneral screening analysis.

Basic rules of forensic chemical analysis

6. For research, you should always use only proven methods and procedures. For qualitative detection, preliminary and confirmatory methods, taking into account their sensitivity and specificity.

7. Each forensic chemical study should be carried out as a quantitative, in which it can turn at any stage of the work.

8. Quantification is carried out in all cases where possible andthere are appropriate determination methods. Number of substances foundrefers to 100 g of sample of the object and is expressed in weight units.

9. All quantitation methods must be validated on thatbiological matrix that will be used for analysis (blood, urine, tissueorgans) according to the scheme of model experiments.

10. Pure reagents should be used

Poison (яд)- is a substance, that may cause poisoning or death when it enters the body because of its detrimental effects on tissues, organs, or biological processes.

Intoxication (poisoning) (*intoxicatio; in- + Greek toxikon poison*) -pathological condition caused by a general effect on the body toxic substances of endogenous or exogenous origin.

Classification of poisons (классификация ядов)

| Chemical classifications (химическая классификация) | | | | |
|--|---|---|--|--|
| Organic substances (alcohols, aromatic amines, ketone, aldehyde,organic solvents (dichloroethane) | Inorganic substances (H2SO4, HNO3, carbon monoxide) | Organoelement (arsine, carbophos, chlorophos, phosphamid) | | |

| + Practical class | ifications (Практическая классификация): | | |
|-------------------------|--|--|--|
| Industrial poisons : | Organic solvents (dichloroethane), gases (propane, butane), | | |
| | aniline, freons, plasticizer etc. | | |
| Pesticides | Hexachlorobenzene, heptachlor, DDT, phosphorus organic | | |
| | compounds | | |
| Medicines | Barbiturates (Barbitone, Phenobarbitone, thiopentone sodium, | | |
| | etc); Tropane alkaloids (Atropine, Scopolamine); 1,4- | | |
| | benzodiazepines (Diazepam, Nitrazepam, etc); Opioids | | |
| | (Trimeperidine); | | |
| Household toxicants | Household chemicals, food supplement (acetic acid) | | |
| Biological, plant and | Is found in plants (Papaver somniferum, atropa belladonna, | | |
| animal poisons | Cannabis), animals и insects (snakes, bees, scorpions) | | |
| Chemical warfare agents | sarin, mustard gas (yperite), phosgene. | | |

| | By selective toxicity: (по избирательной токсичности) |
|-------------------------|---|
| Cardiac poisons | Cardiac glycosides, Animals poisons, barium and potassium salts |
| Nerve poisons | Narcotic analgesics, tranquilizers, phosphorus organic compounds, carbon monoxide, alcohol and its surrogates |
| Liver poisons | alcohols and glycols, poisonous fungi (mushrooms) |
| Renal poisons | Heavy metal compounds , glycols |
| Blood poisons | Aromatic amines, arsine, phosphine, nitrites |
| Gastrointestinal poison | Concentrated acids and alkalis |

| | Classification by level of <u>toxicity :</u> (По степени токсичности) | | |
|---|--|---|--|
| | | | |
| Extremely toxic (DL50 < 15мг/кг) (sarin, mustard gas (yperite), phosgene) | Highly toxic (DL₅₀ 15-150 мг/кг) (dichloroethane, methanol) | Middle toxic (DL _{50,} <u>151</u> -5000 мг/кг) (benzene, <u>chlorophos</u> , | Low toxic (DL ₅₀ > 5000 мг/кг) (hydrocarbons, herbicides) |

| * | Classification by (По методу | methods of isolation: / изолирования) | |
|---|--|---|----------------|
| Mineralization | | Heavy metal compounds (Ba, Pb, Mn, As, | |
| | | Cu, Sb, Bi, Hg, etc) | |
| Steam distillation | | Hydrogen cyanide, | |
| | | Alcohols, ethylene glycol | |
| | | chloroform, dichloroethane, CCl₄ | |
| | | CH₂O, acetone, phenol (hydroxybenzene), acetic acid. | |
| •Pesticides (Hexachlorobenzene, hepta DDT, phosphorus organic compound | | orobenzene, heptachlor, rganic compounds) | |
| Extraction and sorption | | • Barbiturates | |
| _ | | Phenylalkylamine derivatives, | |
| | | Phenothiazine deriv | vatives, |
| | | Cannabinoids | |
| Extraction with water | Extraction with water • acids, alkali, nitrates and nitrites | | s and nitrites |
| Special methods | Fluorine compounds, carbon monoxide, | | |

Intoxication (интоксикация) is a pathological condition. Occurs due to the impact of endogenous or exogenous substances on the body

Classification of intoxications (классификация отравлений):

1. Classification by origin:

- Accidental (accident at work, accidental drug overdose)
- Deliberate (criminals, suicide)

2. Classification by intake of toxicants:

- Endogenous (toxic metabolites are formed and accumulated in the body)
- Exogenous (oral, inhalation, injectable)

3. Classification by duration of effect:

- Acute less than 24 hours (the substance arrives once)
- Subacute within 1 month
- Subchronic from 1 to 3 months
- Chronic more than 3 month (the substance arrives for a long time in small doses) 21

Factors affecting toxicity:

(Факторы влияющие на токсичность)

1. Impact of solubility on toxicity. Insoluble compounds are less toxic because they are worse absorbed

2. Distribution between two immiscible liquids.

3. Impact of acid-bases nature and pH.

- If the poison is a weak acid, than the non-polar organic solvent is acidified
- If the poison is a weak bases than the non-polar organic solvent is alkalized
- **4. Impact of redox potential.** Poisons can oxidize or restore native compounds. It leads to the formation of toxic products.

Targets for toxicants - almost all endogenous connections:

- 1. Macromolecules located either on the surface or inside individual cell types (most often these are intracellular enzymes).
- 2. Nucleic acids (especially DNA)
- 3. Proteins
- 4. Cell membranes
- 5. Enzymes (target mainly for toxic metabolite), because the enzyme it self is responsible for the synthesis of this metabolite.

At the molecular level, toxicity is a chemical interaction between a toxicant and a target molecule.

Theory of toxicity: (Теории токсичности)

Occupation theory of toxicity : the receptors are completely filled with toxicant —> maximum toxic effect

Equilibrium constant shows the affinity of toxicant to the receptor

 $Tox + R \leftrightarrow Tox - R$ $K = \frac{[Tox - R]}{[Tox] \cdot [R]},$

K – Equilibrium constant;
[Tox] – Equilibrium concentration of toxicant;
[R] – Equilibrium concentration of receptor;
[Tox-R] – Equilibrium concentration of product

Kinetic theory of toxicity: the maximum toxic effect is determined by the speed and mechanism of binding toxicant to the receptor.

The internal activity of the toxicant (R/Nзан) expresses the ability to give a toxic effect (ответ организма R) with minimal filling of receptors (Nзан).

Non-specific interactions: Toxicants can:

- Destroy target molecules
- Change the structure of substrates
- Break chemical bonds
- Form new chemical bonds

Example : accumulation of active forms of oxygen (O_2^- ; HOO⁻; HO^{*}) leads to the decay of endogenous substances.

Toxicokinetics is a part of biochemical toxicology, in which studies regularities, as well as qualitative and quantitative characteristics of absorption, distribution, **biotransformation** of xenobiotic in the body and their elimination.



transport of substances across cell membranes









Periods of acute intoxication: (Периоды острого отравления)

1. Hidden period (no symptoms of intoxication);

2. Toxicogenic period (beginning- first symptoms; the end - elimination of poison)

3. Somatogenic period (damage to organs);

4. Recovery period (2 years or more)

