I. GENERAL PHARMACOLOGY

GENERAL PHARMACOKINETICS. PHARMACOGENETICS. GENERAL PHARMACODYNAMICS.

A. Actuality. General pharmacology studies the fundamental laws of pharmacokinetics, pharmacogenetics and pharmacodynamics of drugs and the results of their interaction with the body. Knowing them is necessary for the acquisition and understanding of special pharmacology (mechanisms of action, pharmacological effects, indications, contraindications and adverse reactions) in order to select the appropriate administration routes and medicinal forms. The laws of pharmacokinetics, pharmacogenetics and pharmacodynamics are the basis of experimental and clinical research of new drugs.

B. The purpose of the training. Learning the basic laws of pharmacokinetics, pharmacogenetics and pharmacodynamics.

C. Learning objectives:

a) The student must **know:** General laws of pharmacokinetics (pharmacokinetic parameters, general principles of drug absorption, transport, distribution and purification of drugs), pharmacogenetics (enzymopathies, induction and suppression of enzymes) and pharmacodynamics (types and subtypes of receptors, typical mechanisms of action, types of action, doses and their variations, dosing principles of drugs, safety parameters, the effects of the associated and repeated administration of drugs).

b) The student should **be able to:** characterize the pharmacokinetic parameters, drug administration routes, absorption and transport mechanisms, metabolism and elimination pathways, types of action and typical mechanisms of action of drugs, doses and their variations, dosing principles of drugs , safety parameters, the phenomena triggered by the associated and repeated administration of the drug.

D. Initial level of knowledge required for interdisciplinary integration

General chemistry. The ionization constant of the molecule (pKa). The ionized and non-ionized form depending on the pH values (Henderson-Hasselbach equation). Chemical reactions of oxidation, reduction, hydrolysis and conjugation. Notion about surfactants: ionic, non-ionic and amphoteric.

Bioorganic Chemistry. Amino acids. The proteins. Chemical mediators. Enzymes.

Molecular biology and human genetics. Cell membranes. Transmembrane transport. Genetic mutations.

Anatomy. Digestive system. Stomach and its functions. The small intestine and its functions. Liver and biotransformation processes. Kidneys and their basic functions.

Histology. Cell membranes and their structure. The receptive substrate on the postsynaptic membrane. Physico-chemical properties and molecular structure of the cytoplasmic membrane. Notions about physiological barriers (hemato-encephalic, etc.).

Physiology. Biological membranes. Electrolytic pumps. Transport through the cell membrane. Blood flow. Gastrointestinal tract. Digestion and absorption. Liver function. Body fluids and kidneys. The receivers. Biological rhythms.

Biochemistry. Structural organization of biological membranes. Biochemistry of food and digestion. Transport of substances in the body. Blood biochemistry. Functional biochemistry of the liver and kidneys. Enzymes. Static resting membrane polarization.

Pathophysiology. Membrane processes and their disorders. Disorders of synaptic transmission . Pathophysiology of the digestive system, blood, renal failure and acid-base

balance.

E. Self-training question:

1. Pharmacology, definition. Pharmacology as a discipline. Its relations with other disciplines. The importance of pharmacology for practical medicine.

2. Notion of drug, pro-drug, remedy , placebo, drug . Allopathic and homeopathic medicines, original and generic, orphan, essential, OTC (over the counter) medicines. Notion of active principle (medicinal substance). classification their after origin and principle systemic . The sources of obtaining medicines . Nomenclature medicines .

3. The main stages of developing new drugs, evaluating their effectiveness and harmlessness.

4. Subdivisions of pharmacology (general and special). The fundamental and applied branches of pharmacology.

5. Pharmacokinetics. Pharmacokinetic parameters: bioavailability, plasma concentration, apparent volume of distribution (Vd), biological half-life ($T_{½}$), clearance (Cl), elimination rate constant (Ke). Their characteristic and importance.

6. Classification of drug administration routes. The particularities of the enteral (sublingual, per os (internal), rectal), topical (cutaneous, ocular, auricular, electrophoresis), intracavitary and parenteral (subcutaneous, intramuscular, intravenous, etc.) routes of drug administration. Notion of transdermal therapeutic systems. Peculiarities of the ways of administration in children.

7. Absorption of medicines. Absorption mechanisms. Factors that influence the absorption of drugs. The importance of pH and ionization constant (pKa) for drug absorption. The Henderson-Hasselbach equation for the absorption of acidic and basic drugs. The influence of food on the absorption and effect of drugs. The interaction of medicines with the components of food products. P-glycoprotein and other systems involved in drug absorption. Peculiarities of the absorption of drugs when they are administered together. Peculiarities of drug absorption in children.

8. Penetration of drugs through membranes and biological barriers. The factors that influence the permeability of membranes for drugs. The characteristic of biological barriers. Peculiarities of drug penetration through the blood-encephalic and placental barrier. Accumulation of drugs in tissues.

9. Distribution of medicines in the body (transportation, distribution and storage). The free and bound fraction of drugs in blood and tissues. Peculiarities of drug distribution in children.

10. Biotransformation (metabolism) of drugs in the body. The phases of biotransformation and their importance. Notion of presystemic metabolism (first pass effect) and its importance. Peculiarities of biotransformation in children.

11. Notion about the purification and excretion of medicines. The main ways of drug excretion. Renal excretion: the importance of urine pH and other factors for drug elimination. Renal and hepatic clearance. Elimination of drugs through the digestive tract, lungs, skin, milk. Peculiarities of elimination in children and newborns. "0" and "1" order pharmacokinetic models.

12. Pharmacogenetics. The involvement of genetic factors in drug effects. Enzymopathies. Genetic polymorphism (type of metabolizers). Induction and suppression of hepatic microsomal enzymes. Medicines with enzyme induction and inhibition effect.

13. Pharmacodynamics. Factors that influence the pharmacodynamics of the drug. Pharmacodynamic action and primary action of drugs. The overall pharmacological effect.

Notion about receptors. Drug interaction with receptors. Receptor types and subtypes. The typical mechanisms of action of drugs (mimetic, lytic, allosteric, modification of the functional structure of DNA, RNA macromolecules, membrane permeability and enzyme activity). Types of drug action: local (topical) and systemic (resorptive), direct and indirect (reflective), primary and secondary, selective and non-selective, reversible and irreversible action of drugs.

14. Pharmacography. Dosage. Notion about dose and its varieties. Therapeutic doses: minimum, average and maximum for a (single) intake and for 24 hours, attack dose, maintenance dose, dose for a treatment course. Toxic and lethal dose. Safety parameters (therapeutic index, safety limit, therapeutic range) and their importance. Graphic representation of the dose-effect relationship. The principles of drug dosing in children and the elderly. Biological standardization. Adverse reactions in overdose.

15. Medicines and the factors that influence their action: sex, age, body condition, heredity, biorhythms. Action of the drug during pregnancy (embryotoxic, teratogenic, fetotoxic).

16. Notion about chronopharmacology: chronopharmacokinetics, chronopharmacodynamics. Principles of drug administration according to biological rhythms.

17. The phenomena triggered by the associated administration of drugs: synergism (direct, indirect, infraadditive, summation and potentiation) and antagonism (direct, indirect, unidirectional and bidirectional, physiological, chemical, competitive, etc.). Indifference.

18. Phenomena triggered by repeated administration of drugs: sensitization, tolerance, withdrawal syndrome, rebound effect, functional insufficiency, drug addiction, tachyphylaxis, accumulation and its varieties.

F. Independent work (is done in written form while preparing for the lesson)

1.) Tests (Guidelines for Laboratory Work in Pharmacology).

2.) Tables (recapitulation knowledge)

Table 1 **Speed of appearance of the effect and its duration depend on the route of drug administration**

Drug	Medicinal form	Route of administration	Onset of effect (min)	Duration of effect (min, hours)
Nitroglycerine	Sublingual tablets			
	Tablets for internal use			
	Injectible solution			
	Plaster			
Tramadol	Capsules			
	Injectible solution			
	Suppository			

Table 2 **The comparative characteristic of biotransformation reactions of drugs**

Parameters	Phase I reactions (metabolic transformations)	Phase II reactions (conjugation)
Types of chemical reactions		
Synthetic/non-synthetic reactions		
The enzymes involved in the catalysis of these reactions		

Energy costs (hight/low)		

Table 3 **Examples of receptors and their location**

Receptors	Type	Coupled with G protein	Coupled with enzyme	Coupled with ion channel	Coupled with DNA
	Location (on membrane or intracellular)				
	Examples of receptors				

Table 4 **Choose for each notion with the numbers from** *1* **to** *9 the* **appropriate statements denoted by the letters** *a* **to** *i.*

Dose range	Doses	Definition	Response
Therapeutics	1. Minimal	a) the dose that causes death in 10% of experimental animals	
	2. Medium	b) the minimum amount of drug causing the pharmacological effect	
	3. Maximum	c) the dose that causes intoxication in 100% of experimental animals	
Toxic	4. Minimal	d) the dose that causes death in 100% of experimental animals	
	5. Medium	e) the dose that causes the necessary therapeutic effect in the patient	
	6. Maximum	f) the maximum amount of medicine that does not cause intoxication of the body	
Lethal	7. Minimal	g) the dose that causes intoxication in 10% of experimental animals	
	8. Medium	h) the dose that causes intoxication in 50% of experimental animals	
	9. Maximum	i) the dose that causes death in 50% of experimental animals	

E. Interactive activity:

1) Virtual didactic movie (preparation of minutes and conclusions).

2.) Clinical cases (Guidelines for laboratory work in pharmacology).

3.) Virtual situations (Guidelines for Laboratory Work in Pharmacology).

4.) Solve the case:

What amount of drug will be in the body after 1, 2, and 3 minutes, if it is known that initially the drug was injected intravenously in an amount of 100 mg, and the elimination rate constant of the given drug is 0.1 mg/minute ?