ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF DRUGS TECHNOLOGY

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signature
«27» august 2021y.

METHODICAL DEVELOPMENT OF THE LECTURE

Course: 5 Faculty: Pharmaceutical

Course: **Biopharmacy**

Lecture № 3 Topic: **"Bioavailability of drugs."**

The lecture was developed by:
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The lecture was discussed at the methodical meeting of the department
«27» august 2021y.
Protocol № 1

Odessa – 2021

Lecture: "Bioavailability of drugs" - 2 hours.

The purpose of the lecture: to get acquainted with the modern definition of bioavailability of drugs, the factors that affect it.

Plan

1. Definition of bioavailability.
2. Factors affecting the bioavailability of drugs.
3. Influence of routes of administration on bioavailability.
4. Influence of body temperature and environment
5. Influence of age and sex.
6. Influence of biorhythms.
7. Influence of magnetic field and meteorological factors.
8. Influence of pathological processes and individual features of an organism.
9. Influence of alcohol.
10. The effects of smoking.
11. The effect of drug interactions on bioavailability.

1. Definition of bioavailability.

Bioavailability (BA) is the degree to which a drug is absorbed from the site of entry into the systemic circulation and the rate at which this process occurs.

According to the WHO recommendations, the measure of bioavailability is the ratio (in percent) of the amount of absorption of the drug administered in the test dosage form (A) to the amount of absorption of the same drug administered in the same dose but in the standard dosage form (B), ie BA = (A: B) * 100

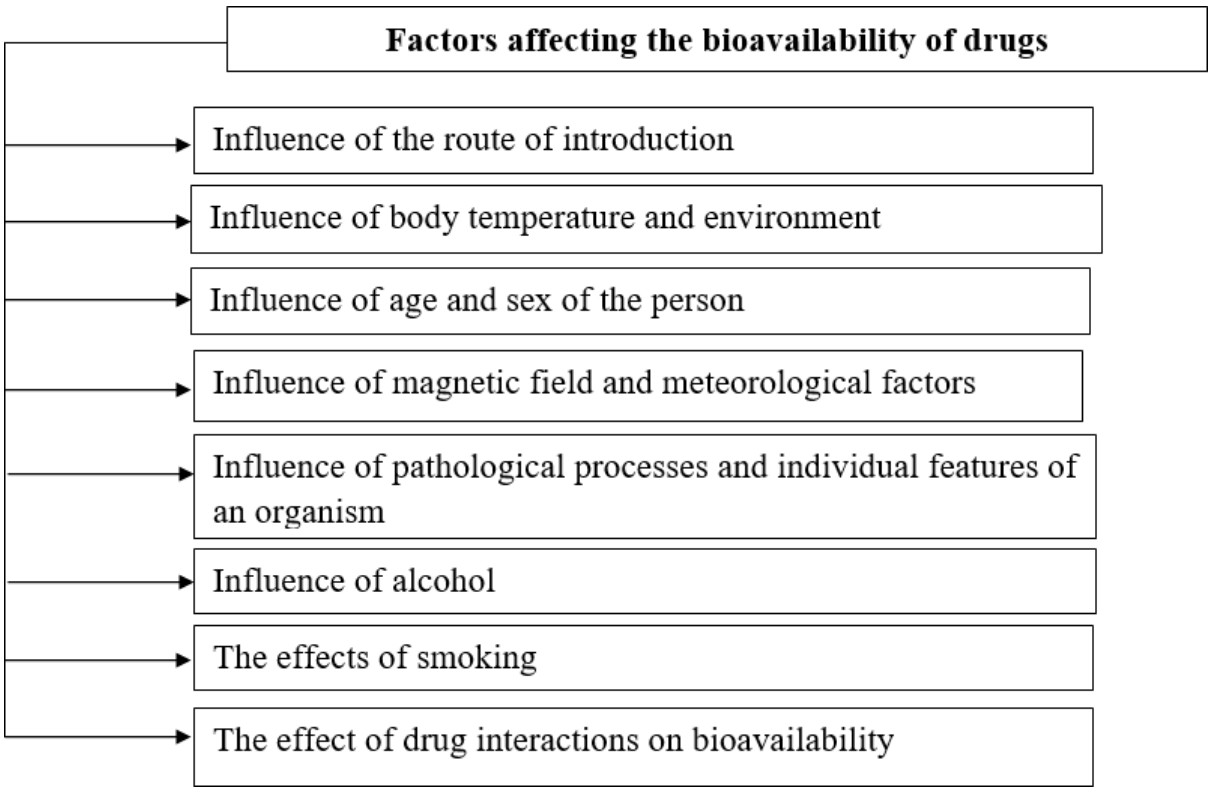
Absolute — **Bioavailability** — *Relative*

General bioavailability

It can be calculated if a solution for internal administration is used as a dosage form, which provides 100% bioavailability.

Characterizes the relative degree of absorption of the drug substance of the study drug and the comparison drug.

Part of the oral dose of the drug, which reached the systemic blood flow in unchanged form and in the form of metabolites formed in the process of absorption as a result of presystemic metabolism ("first-pass effect").



Biopharmacy, along with the pharmaceutical availability test, proposes to establish a specific criterion for assessing the effect of pharmaceutical factors on drug absorption - *bioavailability* - the degree to which a drug is absorbed from the site of entry into the systemic circulation and the rate at which this process occurs.

Bioavailability (DB) is the part of the administered drug that enters the systemic bloodstream by oral, intramuscular, inhalation and other routes of administration. It is obvious that with intravascular administration the DB of the substance will be equal to 100%, and with other routes of administration (oral, rectal, intramuscular, etc.) - much lower and almost never reaches 100%.

According to the WHO recommendations, the measure of bioavailability is the ratio (in percent) of the amount of absorption of the drug administered in the test dosage form (A) to the amount of absorption of the same drug administered in the same dose but in the standard dosage form (B), ie DB = (A: B) · 100. Most often, the bioavailability of drugs is determined by a comparative study of changes in the concentration of the drug in plasma when prescribing the study and standard dosage forms.

When studying the bioavailability of drugs, the most important are the following parameters:

- maximum (peak) concentration of the drug in the blood;
- time to reach maximum concentration;
- area under the curve of change in the concentration of the drug in plasma or serum over time.

The main parameters of pharmacokinetics used in the study of bioavailability of drugs are presented in Fig. 1.

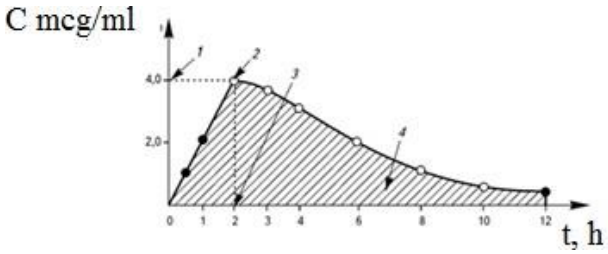


Fig.1. The main parameters of pharmacokinetics used in the study of bioavailability of drugs.

The practical value of the concentration peak is well illustrated in Fig. 2, in which two curves depict the kinetics of the concentration in the blood of the same substance contained in different dosage forms (A and B). The horizontal line indicates the minimum effective concentration (IEC) at which this substance has a therapeutic effect (4 μg / ml). It is seen that in dosage form B, the drug substance, although completely absorbed, but does not have a therapeutic effect, because it does not reach the MEC.

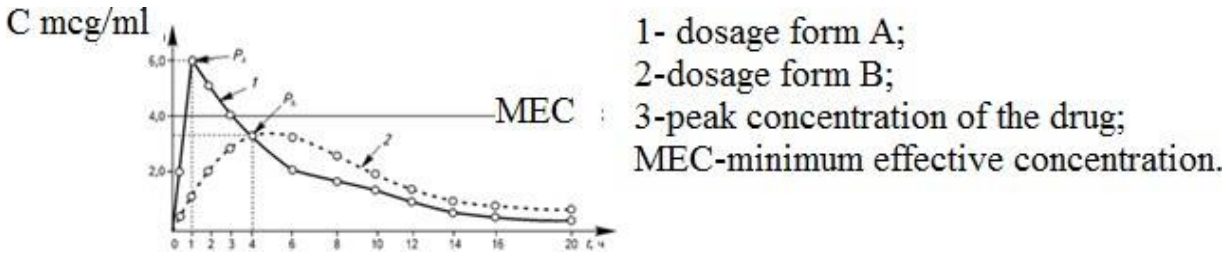


Fig. 2. The dynamics of the concentration (C) of the drug after its use in two dosage forms:

In small. 3 shows the kinetics of a drug substance having an IEC b μg / ml and a minimum toxic concentration (MTC) of 8 μg / ml, when used in two dosage forms A and B. When using dosage form A, the concentration of the substance exceeds the ITC, and therefore it has a toxic effect. When using dosage form B, the drug substance is contained in the blood in therapeutic concentrations, but does not reach toxic concentrations and does not have a harmful effect on the body.

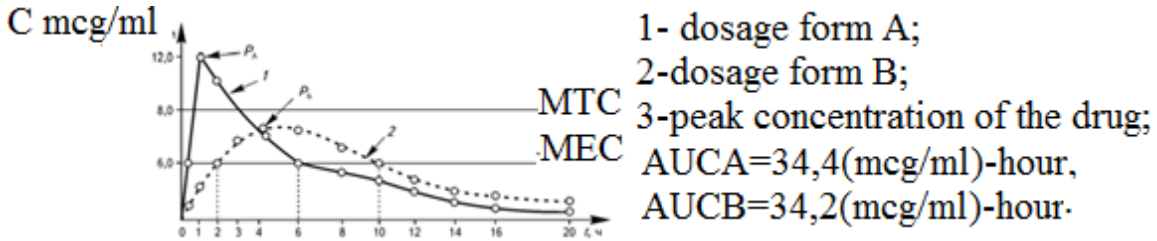


Fig. 3. Determination of the minimum toxic concentration (MTC) and the minimum effective concentration (MEC) of the drug by the dynamics of its concentration in the blood when used in two dosage forms (A and B):

The second important parameter is the time to reach the maximum concentration of the substance in the biological fluid P, as it reflects the rate of absorption of the substance and the rate of onset of therapeutic effect. From fig. 3. it follows that P when

using dosage form A is achieved after 1 hour, and in dosage form B - after 4 hours. Suppose that in this case the drug is a hypnotic. It reaches the minimum therapeutic concentration and has a soporific effect in the first case after 30 minutes, and in the second case - only after 2 hours. At the same time, the effect of the hypnotic substance in the first case (when using dosage form A) lasts 5.5 hours, in the second case (when using dosage form B) lasts 8 hours.

Thus, taking into account the peculiarities of the pharmacokinetics of the same hypnotic, in different dosage forms differ indications for their use. Dosage form A should be used in case of sleep disturbance, while dosage form B - in case of sleep disturbance.

Third, the most important parameter of bioavailability is the area under the curve "concentration - time" (AUC), which reflects the amount of drug that entered the blood after a single injection of the drug.

In small. 3 presents the curves characterizing the bioavailability of two different dosage forms of the same substance. These curves have different shapes, different peaks and different time to reach the IEC. At the same time, the areas under these curves are the same [AUC for dosage form A is 34.4 (μg / ml) -hour, for B - 34.2 (μg / ml) -hour], therefore, both dosage forms provide revenue in blood of the same amount of drug substance. However, they differ in the degree of absorption and the rate of achievement of the IEC of the drug, which has a great influence on both quantitative and qualitative parameters of their therapeutic action, which means that they can not be attributed to bioequivalent drugs. This qualitative characteristic should be taken into account when prescribing and using drugs of similar composition and action, but manufactured by different pharmaceutical companies.

Fig. 4. The relative bioavailability of the drug when used in three dosage forms:

In small. Figure 4 shows the curves that reflect the kinetics of the same substance when used in three different dosage forms - A, B and B.

The area under the curve that characterizes dosage form A is larger than under curve B and much larger than under curve B. It follows that dosage form A provides absorption into the blood of the drug much better than dosage forms B and B.

Thus, to compare different generic drugs, dosage forms, to address the issue of replacing the drug with an analogue, it is necessary to take into account the parameters of bioavailability. Differences in the degree of absorption and the rate of reaching the maximum concentration of the drug can have a significant impact not only on the quantitative parameters of the therapeutic effect of the drug, but also on its qualitative characteristics.

2. Factors affecting the bioavailability of drugs

The drug immediately enters the systemic bloodstream only when administered intravascularly. With all other methods of administration, this is preceded by a number of different processes. First of all, the drug substance must be released from the dosage form - tablets, capsules, suppositories, etc. The tablets are first destroyed, only then the drug goes into solution. The capsule first dissolves the shell, then releases the drug, which only then passes into solution. When administered as a suspension, the drug substance dissolves under the influence of body fluids (saliva, gastric juice, bile, etc.). The base of the suppositories melts in the rectum, and then the drug becomes capable of dissolving and absorbing. The rate of absorption may decrease and the duration of action may increase if the drug is administered in the form of insoluble complexes, which then disintegrate in the injection area, forming a form soluble in water. An example is benzylpenicillin sodium, protamine-zinc-insulin.

The drug, administered orally or rectally, is absorbed by the capillaries of the gastrointestinal tract (GI tract), and then through the mesenteric veins enters the portal vein and liver. If the drug is rapidly metabolized in the liver, then some of it is converted into metabolites before it is found in the systemic circulation. This position is even more true for drugs that are metabolized in the intestinal lumen, its wall or mesenteric veins. This phenomenon is called presystemic metabolism or first-pass effect (EPP).

According to physiologists, the greatest distance at which cells in tissues defend from capillaries is about 0.125 mm. Since the cells of the human body have an average diameter of 0.01 mm, the drug molecule after entering the systemic bloodstream must overcome the biological barrier, consisting of approximately 10-12 cells, before entering into a specific interaction with the receptor. In order to get into the brain, eye, breast milk and a number of other organs and tissues, drugs must also overcome special biological barriers, such as blood-brain, hematoophthalmic, placental and others.

Thus, when drugs are administered extravascularly, a number of chemical-pharmaceutical and medical-biological factors are able to have a significant impact on its bioavailability. In this case, physiological factors are important both in themselves and in interaction with pharmaceutical factors.

Consider the most significant medical and biological factors that can affect the bioavailability of drugs, and hence their therapeutic efficacy and toxicity.

3. Influence of routes of administration on bioavailability

Oral route of administration of drugs

Most drugs are administered orally, ie by mouth. This way of drug administration is the simplest and most convenient. At the same time, the number of factors that may affect the bioavailability of drugs is the largest in this way of introduction.

Influence of enzymes of the gastrointestinal tract . Drugs affect the body differently, depending on when they are taken: before meals, during or after meals, due to changes in the pH of the gastrointestinal tract, the presence of various enzymes and active substances released from the bile to ensure the digestive process .

During and after meals, the acidic environment of the stomach reaches pH = 2.9 ... 3.0, and the small intestine - 8.0 ... 8.4, which significantly affects the ionization, stability of drugs, the speed of their passage through digestive tract and absorption into

the blood. Thus, acetylsalicylic acid at a gastric pH of 1 to 3 is almost completely in non-ionized form and as a result (due to the high solubility in lipids) is almost completely absorbed. Taking aspirin with food increases the amount of the drug, which is converted into a salt form, the rate of absorption in the stomach is reduced to values approximately coinciding with the rate of absorption of aspirin in the small intestine, and bioavailability is generally reduced.

Erythromycin, benzylpenicillin, pancreatin, pituitrin, insulin and a number of other drugs are inactivated under the influence of acidic environment and gastric enzymes. Hexamethylenetetramine is completely decomposed into ammonia and formaldehyde.

Therefore, most orally administered drugs are significantly affected by enzymes and various highly active substances of the gastrointestinal tract, released during and after meals, which can significantly affect their bioavailability.

Influence of composition and temperature of food .

The composition and temperature of food have a great influence on the effectiveness of drugs. Ordinary mixed food contains substances of plant, animal and mineral origin: proteins, fats, carbohydrates, amino acids, fatty acids, glycerin, tannins (in tea, persimmons), caffeine (in tea, coffee), serotonin (in nettles, peanuts, bananas). , pineapples), tyramine (in cheese, bananas, beans, herring, coffee, beer, wine, chicken liver), oxalates (in rhubarb, celery, sorrel, spinach), sterols, phytosterols, heavy metal ions and other chemically and pharmacologically active substances. Depending on the composition of food in different ways affects the peristalsis and secretory function of the digestive tract, which depends on the degree and rate of absorption of drugs.

Protein foods (eggs, cheese, milk, peas, beans) reduce the pharmacological effect of digitoxin, quinidine, cimetidine, caffeine, theophylline, tetracycline and penicillin, anticoagulants, cardiac glycosides and sulfonamides.

Fats (especially those containing higher fatty acids) reduce the secretion of gastric juice, slow down the peristalsis of the stomach, which leads to delayed food processes and transportation of food mass. Under the influence of foods rich in fat, the absorption of many drugs is significantly increased, especially fat-soluble, such as anthelmintics, anticoagulants, sulfonamides, griseofulvin, anaprilin, diphenine, fat-soluble vitamins A, D, E, carbamazepine, lithium metro, and lithium, and lithium. . Deficiency in eating fats slows down the metabolism of ethylmorphine hydrochloride. Preliminary intake of fatty foods reduces the activity of salol and besalol.

Influence of the nature of the liquid used for drinking drugs.

The nature of the liquid with which the drug is washed plays a role in the bioavailability of drugs. Often, to mask the unpleasant taste and smell of drugs, use a variety of fruit or vegetable juices, tonics, syrups, milk. Most fruit and vegetable juices are acidic and can destroy acid-fast compounds, such as ampicillin sodium, cycloserine, erythromycin, benzylpenicillin, potassium salt. Juices can slow down the absorption of ibuprofen, furosemide, enhance the pharmacological effect of adebit, barbiturates, diacarb, nevigramon nitrofurans, salicylates.

When sweetening drugs with syrups or milk sugar, the absorption of isoniazid, ibuprofen, calcium chloride, tetracycline hydrochloride, furosemide is sharply slowed

down. Some drugs that have an irritating effect on the mucous membrane of the gastrointestinal tract, washed down with milk. Medicines are mixed with milk and dairy products for infants. Some patients, taking medication, do not drink them at all, which is not recommended, because the capsules, tablets, pills, sticking to certain parts of the inner surface of the esophagus and gastrointestinal tract, are destroyed before reaching the site of absorption. In addition, they cause irritation at the site of adhesion, and the lack of sufficient fluid delays their absorption.

Rectal route of administration of drugs

The rectal route of administration of drugs (through the rectum) ensures their rapid absorption (after 7 - 10 minutes). It is used for both local and general action. At a rectal way of administration of medicinal substances in 5-15 min. the minimum therapeutic concentration is created in blood. This is due to the presence in the rectum of a dense network of blood and lymphatic vessels, good absorption of drugs, soluble in both water and fat, through the mucous membrane of the rectum. Substances, absorbed in the lower part of the rectum, through the inferior hemorrhoidal veins enter the systemic bloodstream, bypassing the hepatic barrier. The fact that the rectal route of administration of drugs are not destroyed by the enzyme system of the liver as a result of the "primary effect", significantly increases their bioavailability compared to oral administration.

The process of intestinal absorption is influenced by the autonomic nervous system (adrenergic agonists stimulate absorption, and cholinergic antagonists - secretion), endocrine system, biologically active peptides. Endocrine, autonomic nervous and neuropeptide systems also regulate the motor activity of the colon, which, in turn, determines the duration of the drug in the intestine. In addition, a number of diseases of the rectum (hemorrhoids, cracks in the anorectal region, proctitis) impair the bioavailability of drugs administered rectally.

Inhalation route of drug administration

During the inhalation route of administration, the drug is rapidly absorbed into the systemic bloodstream through the bronchial mucosa without affecting the primary metabolism in the liver. With this route of administration, the bioavailability of drugs may be affected by concomitant diseases of the bronchopulmonary system, smoking (as a factor contributing to the development of chronic bronchitis with appropriate restructuring of the bronchial wall structure), and circulatory status in the bronchopulmonary system.

4. Influence of body temperature and environment

The increase in body temperature is accompanied by a sharp excitation of the CNS, respiration and blood circulation, increased metabolism. Excessive sweating leads to dehydration, blood clotting, decreased volume of circulating fluid, electrolyte imbalance. All this, in turn, affects the processes of absorption, distribution and metabolism of drugs, their bioavailability after oral administration.

With increasing absorption temperature, metabolism and transport of drugs proceed faster, and with decreasing - slow down. Local cooling of body tissues leads to vasospasm, resulting in a sharp slowdown in absorption, which should be borne in mind when local administration of the drug. The influence of temperature factor on the

pharmacokinetics of drugs must be taken into account in clinical practice in cases where drugs are prescribed to patients with severely impaired thermoregulation.

5. Influence of age and sex

A person's age also affects the bioavailability of drugs. For young patients are characterized by higher rates of absorption, excretion, the shortest time to reach the maximum concentration of drugs; for the elderly - a higher value of the half-life of drugs.

When prescribing drugs to children, it is important to remember that in children under one and a half years of age, the bioavailability of drugs taken orally is only slightly different from that of adults. However, their absorption (both active and passive) is very slow. As a result, small concentrations are created in the blood plasma, often insufficient to achieve a therapeutic effect. In children, the delicate, easily irritated mucous membrane of the rectum, because the reflexes that occur, lead to rapid bowel cleansing and reduced bioavailability of drugs.

6. Influence of biorhythms

One of the most powerful factors influencing a person and the effectiveness of drug therapy is also the action of biorhythms. Every cell of our body experiences time - the alternation of day and night. For a person is characterized by an increase during the day and a decrease in night physiological functions (heart rate, minute blood volume, blood pressure, body temperature, oxygen consumption, blood sugar, physical and mental performance). Biological rhythms cover a wide range of periods: age, annual, seasonal, monthly, weekly, daily. They are all strictly coordinated. The circadian, or round-the-clock, rhythm at the person is shown, first of all, in change of the periods of a dream and wakefulness. There is a biological rhythm of the body with a much lower frequency than the daily, which affects the reactivity of the body and affects the action of drugs. Such, for example, hormonal rhythmics (female menstrual cycle).

During the day there is a different sensitivity of the body to optimal and toxic doses of drugs. The experiment found a 10-fold difference in mortality of rats from elenium and other drugs in this group at 3 o'clock in the morning compared with 8 o'clock in the morning. Tranquilizers show maximum toxicity in the active phase of the day, coincide with high motor activity. Their lowest toxicity was observed during normal sleep. Acute toxicity of adrenaline hydrochloride, ephedrine hydrochloride, mezaton and other adrenomimetics increases during the day and decreases significantly at night. And the acute toxicity of atropine sulfate, platyphylline hydrotartrate, metacin and other cholinolytics is much higher at night, in the inactive phase of the day. High sensitivity to sleeping pills and anesthetics is observed in the evening, and to anesthetics in dentistry - at 14-15 o'clock in the afternoon (at this time it is recommended to remove teeth).

7. Influence of magnetic field and meteorological factors

- significantly affect the higher centers of nervous and humoral regulation, biocurrents of the heart and brain, the permeability of biological membranes. Men are more sensitive to the activity of the Earth's magnetic field than women. Patients with disorders of the nervous and cardiovascular systems are most sensitive to magnetic

storms in the Earth's atmosphere. In the days of magnetic storms, they have an exacerbation of the disease, there is a hypertensive crisis, cardiac arrhythmias, angina attacks, reduced efficiency, and so on. In turn, changes in the work of the heart, the intensity of blood circulation and, above all, the permeability of biomembranes can significantly change the bioavailability of drugs with different routes of administration, both in the direction of its reduction and increase.

Meteorological factors (absolute humidity, atmospheric pressure, wind direction and strength, average daily temperature, etc.) affect the elasticity of blood vessels, viscosity and clotting time. A decrease in atmospheric pressure by 1.3-1.6 kPa (10-12 mm Hg) can lead to vascular disorders, rainy weather causes depression.

8. Influence of pathological processes and individual features of an organism

Significant in the body's response to drugs is its initial state. The influence of pathological conditions and diseases of the gastrointestinal tract and liver on the processes of absorption and metabolism of drugs are discussed above.

First of all, these are pathological processes that promote free radical (peroxide) oxidation of lipids, inflammatory processes that lead to the activation of phospholipases and their hydrolysis of membrane phospholipids. Also important are the processes that are accompanied by changes in electrolyte homeostasis of tissues, which causes mechanical (osmotic) stretching of membranes. General stress reactions of the body also lead to a mandatory change in the properties of all biological barriers, which inevitably affects the bioavailability of drugs and the effectiveness of drug therapy in patients of this category.

9. Influence of alcohol

Alcohol adversely affects the therapeutic effect of many drugs and is the cause of dangerous complications. Ethanol affects the pharmacodynamics and pharmacokinetics of drugs in different ways. The bioavailability is directly affected by the following factors: changes in the permeability of histohematological barriers due to impaired fluidity of lipid membranes when interacting with ethanol; changes in the structure and function of cell membranes, impaired penetration of drugs through biomembranes; change in the structure and function of enzymes (acetylcholine esterase, mitochondrial electron transport chain enzymes); increased secretion of gastric mucus and decreased absorption of drugs in the stomach; switching the microsomal system of the nonspecific enzymatic system of the liver (MEOS - microsomal ethanooxidation system) to the oxidation of ethanol, resulting in a decrease in the level of oxidation of other endogenous and exogenous ligands; induction of liver microsomal enzymes and, as a consequence, changes in the rate and level of biotransformation of drugs.

At simultaneous appointment of drugs and ethyl alcohol their interaction can occur at once on several mechanisms that has important clinical value. The effect of the interaction of alcohol and drugs on the body depends on their concentration in the blood, pharmacodynamic properties of drugs, dose and time of administration. In small quantities (up to 5%) alcohol increases the secretion of gastric juice, and in concentrations of more than 30% clearly reduces its secretion and inhibits digestive

processes. The absorption of many drugs increases as a result of increasing their solubility under the influence of ethanol. Possessing lipophilic properties, alcohol facilitates the penetration of drugs through the phospholipid membranes of cells, and in higher concentrations, affecting the gastric mucosa, further increases the absorption of drugs. As a vasodilator, ethanol accelerates the penetration of drugs into tissues. Inhibition of many enzymes, which occurs with alcohol consumption, enhances the effect of drugs and leads to severe intoxication at the usual therapeutic doses. This applies to neuroleptics, analgesics, anti-inflammatory, hypnotics, diuretics, as well as antidepressants, insulin, nitroglycerin. The combination of the above groups of drugs and alcohol is accompanied by severe poisoning, often fatal.

10. The effects of smoking

The action of drugs can be affected by substances entering the body during smoking. Nicotine as an H-cholinomimetic leads to the activation of sympathetic and parasympathetic ganglia, the cerebral layer of the adrenal glands, CNS dysfunction. Stimulation of the cerebral layer of the adrenal glands leads to narrowing of peripheral blood vessels, which disrupts the blood supply to many organs and tissues. Nicotine, benzpyrene and their derivatives alter the activity of metabolic enzymes. Smoking stimulates the oxidative metabolism of phenacetin, propranolol, theophylline, noxiron, aminazine, diazepam, resulting in reduced efficiency. Smoking reduces the therapeutic effect of dexamethasone, furosemide (lasix), propoxyphene and oral contraceptives. Flavored cigarettes contain coumarins, which can enhance the effect of anticoagulants - coumarin derivatives

In a number of cases, the effect of smoking on the bioavailability and therapeutic efficacy of drugs requires further study. Thus, when prescribing drugs and assessing their therapeutic efficacy and toxicity, it is necessary to take into account the effects of numerous external and internal environmental factors.

11. The effect of drug interactions on bioavailability

Such interaction means a qualitative and quantitative change in the effect of one drug under the influence of another. From a practical point of view, it is important to remember that even pharmacologically indifferent components of a drug can interact with another substance, affecting its bioavailability. The drug is also able to interact with itself. When re-ingested, it can induce microsomal oxidation of a foreign substance and thus accelerate its own metabolism (a classic example is barbiturates). Medications can also worsen their own effects on organs (an example is the emergence of opiate tolerance). In clinical practice, the phenomenon of drug interactions must be constantly considered for the following reasons: - almost every hospitalized patient during a hospital stay receives several drugs (sometimes up to 40! Substances prescribed to one patient), numerous finished drugs are a combination of two or more substances, a significant number of patients in outpatient treatment, consume drugs such as laxatives, analgesics, hypnotics, etc. Of all possible interactions, only about 1-10% pose a risk of adverse effects, but the risk of mutual reduction in efficiency is significantly higher. New reports of drug interactions should always be treated with great care. The number of possible interactions at first glance is extremely large,

although not everyone has clinical significance. There are three types of interactions: pharmaceutical, pharmacokinetic and pharmacodynamic.

Questions for self-control

1. Biopharmacy as a scientific discipline and its importance in the development of composition and technology of dosage forms.
2. History of biopharmacy development.
3. Basic concepts and terms of biopharmacy.
4. The main tasks of biopharmacy at the present stage and their role for practical health care.
5. The concept of pharmaceutical factors influencing the therapeutic efficacy of drugs, their classification.
6. The physical state of drugs and excipients in dosage forms and its effect on the rate of release and absorption of drugs.
7. The influence of the physical state of drugs on the pharmacological action.
8. The influence of the degree of dispersion of drugs on the therapeutic effect of drugs.
9. The effect of crystal structure and polymorphism of drugs on the pharmacological activity of drugs.
10. The influence of the nature of the solvent, solubility, degree of viscosity and pH of the medium on the absorption of drugs.
11. The degree of purity of the drug and its effect on pharmacotherapy.
12. Dependence of therapeutic activity of drugs on the type and quality of packaging.

Main:

. 1. Біофармація : підруч. для студентів закл. вищ. освіти / О. І. Тихонов [та ін.] ; за ред. О. І. Тихонова. – 2-ге вид., перероб. і допов. – Харків : НФаУ: Золоті сторінки, 2019. – 224 с

2. Настанова СТ-Н МОЗУ 4242-7.1:2005 «Лікарські засоби. Настанова з клінічних досліджень. Дослідження біодоступності та біоеквівалентності» - Київ, 2018.

3. Настанова СТ-Н МОЗУ 4242-7.1:2005 «Лікарські засоби. Настанова з клінічних досліджень. Дослідження біодоступності та біоеквівалентності» - Київ, 2018.

4. Настанова СТ-Н МОЗУ 42-7.2:2018 Лікарські засоби дослідження біоеквівалентності. – Київ, 2018. – 77 с.