Technology of drugs department

Discipline "*Biopharmacy*"

Bioavailability and methods of its determination. The influence of biological factors and environmental factors on bioavailability. The influence of the type of dosage form in the process of releasing active pharmaceutical ingredients from drugs

LECTURE FOR ENGLISH SPEAKING STUDENTS OF SPECIALTY «PHARMACY»

Lecturer: ***ass. prof. Kovalev V.V.***

Plan of the lecture

1. Definition of bioavailability.
2. Measure of bioavailability.
3. Absolute bioavailability.
4. Relative bioavailability.
5. Total bioavailability.
6. Main parameters of bioavailability
7. Main parameters of pharmacokinetics
8. Dynamics of medicinal substance concentration (C) after its administration in 2 medicinal forms (A and B) with soporific activity

Questions for individual work

Modern types of modified dosage forms.

Recommended Books

- Biopharmaceutics. Practical handbook for English students of the 5th year, speciality “Pharmacy”: a handbook for the work of students / Edited by acad. A.I. Tikhonov. - Kh.: PH of NUPh, 2011. – 68 p.
- British Pharmacopoeia. – London: The Stationery Office, Vol. III, 2009. – P. 7533-7614. European Pharmacopoeia. Sixth edition. – Strasbourg: Council of Europe, Vol.1., 2008. – P. 1063-1084.
- Shargel, L. Applied Biopharmaceutics & Pharmacokinetics / L. Shargel, A. Yu, S. Wu-Pong. – 6 ed. – New-York: McGraw-Hill Medical, 2012. – 811 p. Mark P. Mathieu. PAREXEL Biopharmaceutical R&D Statistical Source-book 2014-2015 / Mark P. Mathieu. – Parexel Intl Corp., 2014. – 421 p.
- www.tl.nuph.edu.ua – site of Drugs Technology Department.
- Training portal http://pharmel.kharkiv.edu – distance learning center of NUPh.
- http://dspace.nuphedu.ua – electronic archive of NUPh.

1. Definition of bioavailability

Bioavailability (BA) is a part of introduced medicinal substance, which gets into the bloodstream by oral, intramuscular, inhalation and other routes of introduction.

Intravascular route of introduction assures 100 % bioavailability of medicinal substances.

The other routes of introduction do not provide such high level of bioavailability.

2. Measure of bioavailability

According to the World Health Organization of U.N.O., *the measure of bioavailability* is the ratio (%) of the quantity of absorbed medicinal substance, which was prescribed in a certain medicinal form under study (A), to the quantity of the same absorbed medicinal substance, that was prescribed in the same dose but in the standard medicinal form (B).

$$BA = \frac{A}{B} \bullet 100,\%$$

3. Absolute bioavailability

Absolute bioavailability (ABA) is defined by measuring the area under curve which shows changes of medicinal substance concentration in plasma or blood serum during time. In this case, solution for intravascular introduction must be taken as the standard medicinal form.

Area under curve (AUC) is the area of the figure, which is limited with pharmacokinetic curve and axes of coordinates

$$\mathbf{AUC = C_0/K_{el}},$$

where C_0 is initial concentration of medicinal substance in blood serum; K_{el} is elimination constant.

4. Relative bioavailability

Relative bioavailability (RBA) describes a relative degree of medicinal substance absorption out of the medicine under study and the reference medicine. In this case, any medicinal form with the same medicinal substance in the same quantity be taken as the standard one.

Relative bioavailability is defined for different series of medicines when changing technology of preparation and for medicines of the similar composition prepared by different companies.

Usually RBA is defined for medicines with the same route of introduction but it is possible to define it for medicines of different medicinal forms as well.

5. Total bioavailability

Total bioavailability is a part of medicine's dose taken in, which has reached the bloodstream in intact form and in form of metabolites, that are formed during the process of absorption and as the result of presystemic metabolism ("first-pass effect ").

Total bioavailability is defined for medicines which are subjected to metabolism in liver when taken in peroral route.

BIOAVAILABILITY is a measurement of the rate and extent to which a drug reaches the systemic circulation.

It is denoted by the letter *f* (or, if expressed in percent, by *F*).

Factors which has influence on the release of drugs

- When MS has moved to a soluble form suitable for absorption at the injection site, it still has to overcome a series of membranes before penetrate the capillary bed and enter the systemic blood flow.

  With the introduction of drugs into the body through non-vascular, a number of variables may affect their bioavailability.

Factors which has influence on the release of drugs

The extent of absorption of drugs affecting various factors, especially factors of physiological and pharmaceutical agenda that ultimately determine the bioavailability of the drug. In each case, the factors affecting the processes of absorption, biotransformation, elimination, can alter the biological equivalence of drugs and thus their therapeutic equivalence.

Factors which has influence on the release of drugs

BIOAVAILABILITY of drugs depends on:

- Disintegration
- Dissolution
- Release

Factors which has influence on the release of drugs

Determination of the parameters above for MS is mandatory of the development of new drugs, as well as their quality control in manufacturing.

Ideally, the process of disintegration, dissolution and release should be investigated by such methods that would provide results comparable to methods in vivo.

Main parameters of bioavailability

- C_{max} - Maximum (peak) of medicinal substance concentration in blood;
- t_{max} - Time of reach of maximum concentration;
- ***AUC*** - Area under curve of medicinal substance concentration changing in plasma or blood serum in time.

Main parameters of pharmacokinetics

When describing pharmacokinetics processes mainly the following parameters are used:

- **$T_{0,5}$ – half-period of the medicines;**
- **K_{el} – constant of elimination;**
- **Cl_t – systemic clearance;**
- **V_d – volume of distribution;**
- **MKT – average period of medicine's content in the blood;**
- **ABA, RBA (or f) – absolute or relative bioavailability of the medicine.**

Main parameters of pharmacokinetics

The main parameters of pharmacokinetics which are used when studying bioavailability of medicines: 1 – maximum concentration (C); N – peak; 2 – time (t) of maximum concentration reach; 3 – area under curve “concentration – time”.

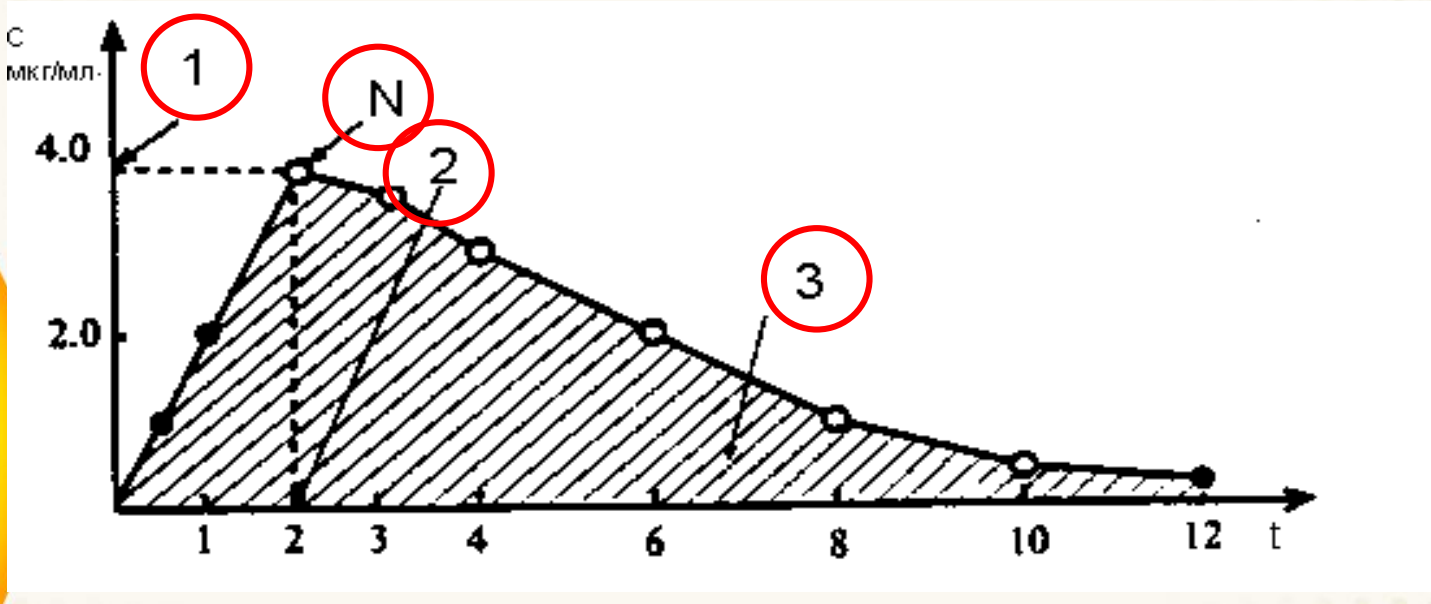


Fig. 1

Key indicators of bioavailability of drugs

- Pharmacokinetic curves have different shapes , different time to reach the IEC . At the same time, the area under these curves are identical (AUC dosage form for A is equal to 34.4 micrograms / ml * hr for B - 34.2 mg / mL * h), hence both formulations provide admission to the same number of blood drug substance. However, they differ in the degree of absorption and rate of achievement of MEK , which greatly influences both the quantitative and qualitative parameters of their therapeutic action , so they not bioequivalent.

Key indicators of bioavailability of drugs

Thus , the indicator " area under the curve " should be considered when prescribing and use of LP generics (similar compounds and action, but made by different pharmaceutical companies).

Thus, to compare different LP in solving the issue of replacing the drug must be considered in analog basic pharmacokinetics.

Dynamics of medicinal substance concentration (C) after its administration in 2 medicinal forms (A and B) with soporific activity

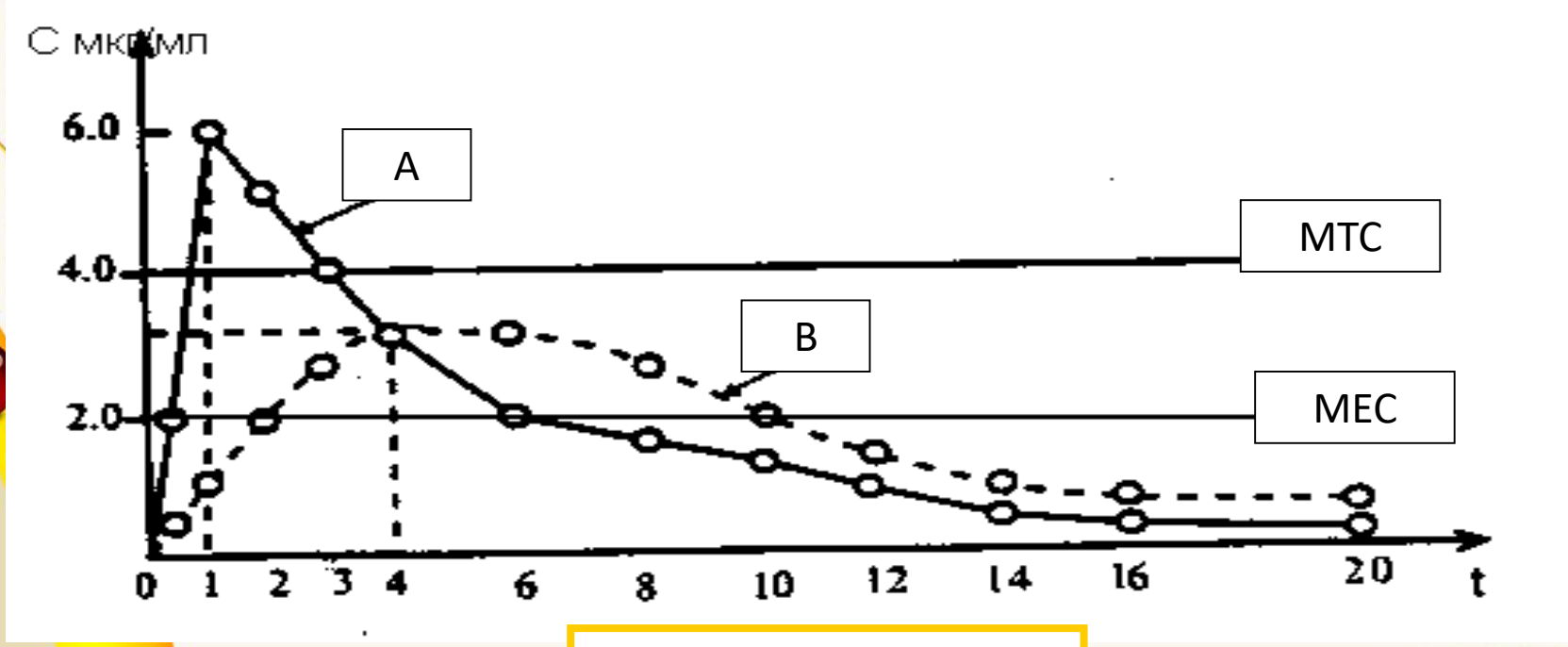


Fig. 2

- Minimal effective concentration (MEC)
- Minimal toxic concentration (MTC)

Dynamics of medicinal substance concentration (C) after its administration in 2 medicinal forms (A and B)

As seen from fig. 2, medicinal substance in both medicinal forms A and B shows good therapeutic effect as they both reach MEC. However, concentration of medicine A exceeds MTC, so it will cause side effects and toxic reactions in the organism of the patient. Unlike medicine A, medicine's B concentration reaches MEC but not MTC, so it will have high therapeutic effect with minimum side effects.

Dynamics of medicinal substance concentration (C) after its administration in 2 medicinal forms (A and B)

- It is also seen that time of maximum concentration (C_{max}) of medicine A is reached in 1 h., when for medicine B it is reached in 4 h. Medicinal substance in these forms has soporific activity. It reaches MEC and shows its pharmacological activity in the forms A – in 30 min. and in the form B – in 2 h. Duration of soporific effect is 5,5 h. (for medicine A) or 8 h. (for medicine B).
- Thus, when taking into account the peculiarities of pharmacokinetics of the same medicinal substance with soporific activity in different medicinal forms, it is reasonable to choose medicine A for treatment of malfunction of falling asleep and medicine B – for treatment of malfunction of sleep duration.

Key indicators of bioavailability of drugs

- The practical value of the index of the peak concentration is well illustrated picture in which the two curves represent the kinetics of the concentration levels of the same LB containing in different dosage forms (A and B).

The horizontal line marked by the minimum effective concentration (IEC), in which the substance has a therapeutic effect (2 mg / ml).

Key indicators of bioavailability of drugs

- Thus it is clear that MS in the dosage form A and B have a therapeutic effect because its concentration reaches MEK. When using the dosage form and concentration than LR ITC and therefore has a toxic effect. In the application of LR in the form of B substance contained in the blood therapeutic concentrations, but without reaching toxic concentration (MTC), has actions that damage the body.

4.Методи визначення лікарських речовин в біологічних рідинах

Methods for assessing MS in medicines

“in vitro”

CORRELATION

“in vivo”

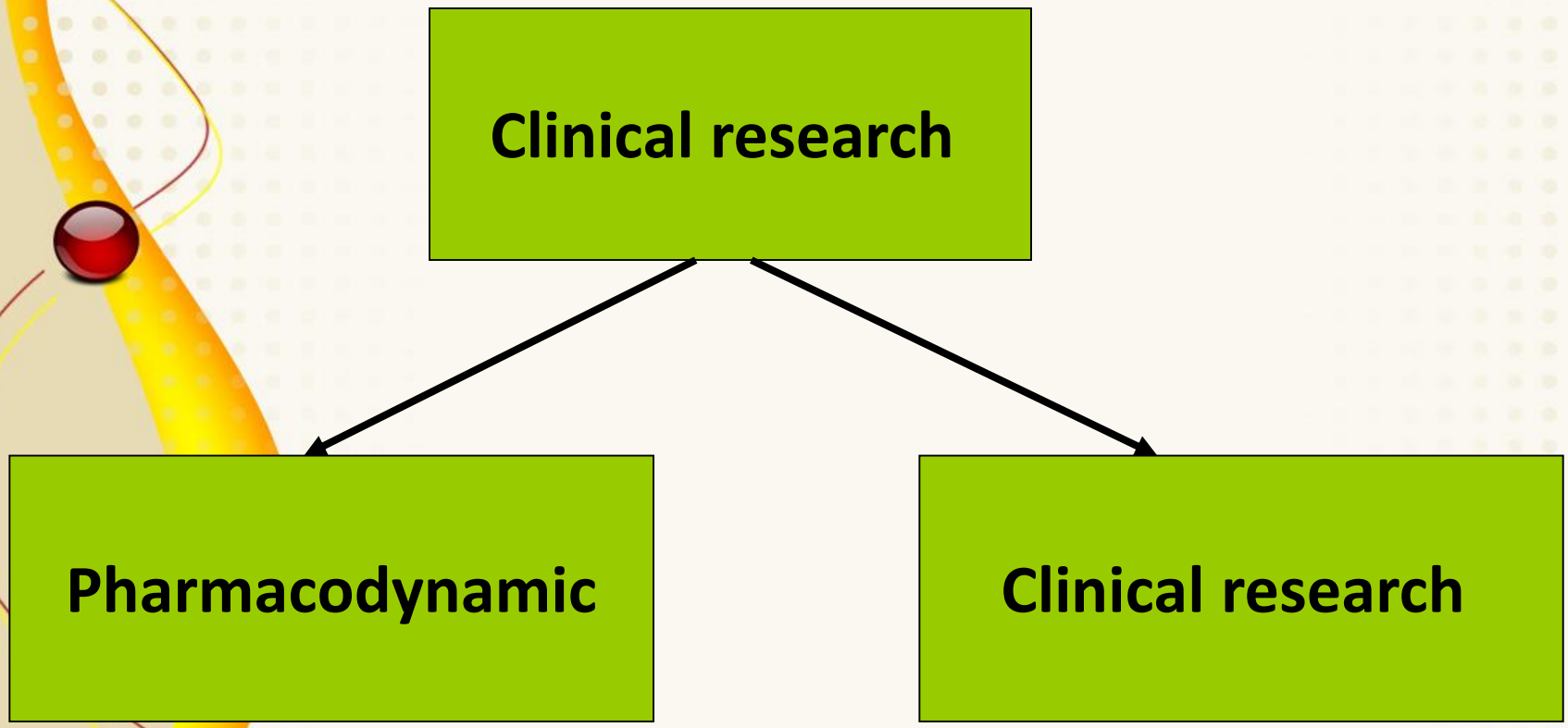
Determination MS in an environment in which a substance diffuses

Determination of Liquids in medicines

Methods for determination of drugs in biological fluids

- Experiments "in vivo" determination is made in LR bioliquids (blood, urine , saliva , milk, fecal masses) and other tissues and organs. Quite clear that the study "in vivo" can not be used for mass appraisal quality dosage forms. For these purposes need simple, fast, accurate methods "in vitro", which allows to conduct multiple studies . Methods "in vitro" enables more deeply investigate the mechanism of absorption.
  DB drugs determined in human studies , which are carried out instructions with respect to diet , depending on the type of study drugs . Conducted trial sequential sampling of biological fluids for strictly specified period and calculated concentration of drug samples .

Methods for determination of drugs in biological fluids



Conclusion

- Biological availability is a condition that allows the drug substance that is introduced into the body to reach its place of action.
- Relative bioavailability - expressed as a percentage of the amount of drug substance released from the dosage form, which, after its administration, reaches the receptor in an amount sufficient to exhibit a biological effect.
- Absolute biological availability is the amount of medicinal product administered intravenously or intravenously in the dosage form that enters the bloodstream without affecting the effect of the first passage through the liver (the effect of the "first pass") or after the correlation of this effect, as well as the velocity of the process.
- Physiological accessibility is synonymous with "biological accessibility" or "bioavailability".

Thank you for your attention!