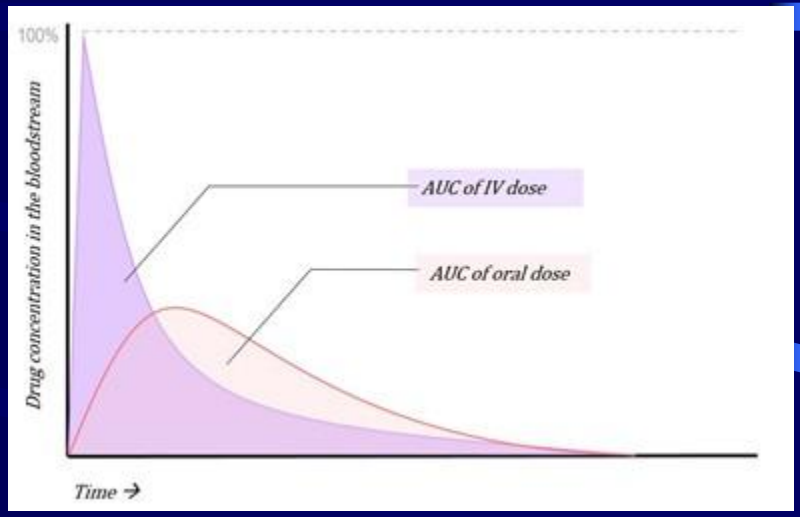
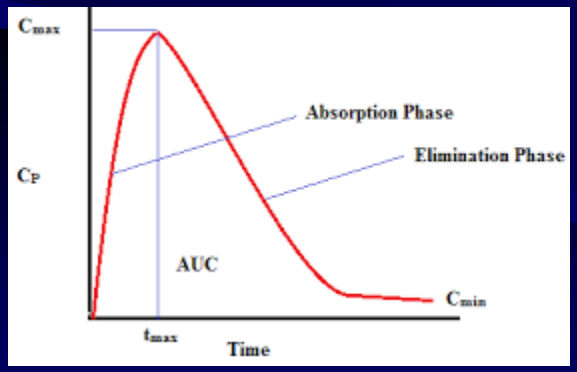
Pharmacokinetic parameters





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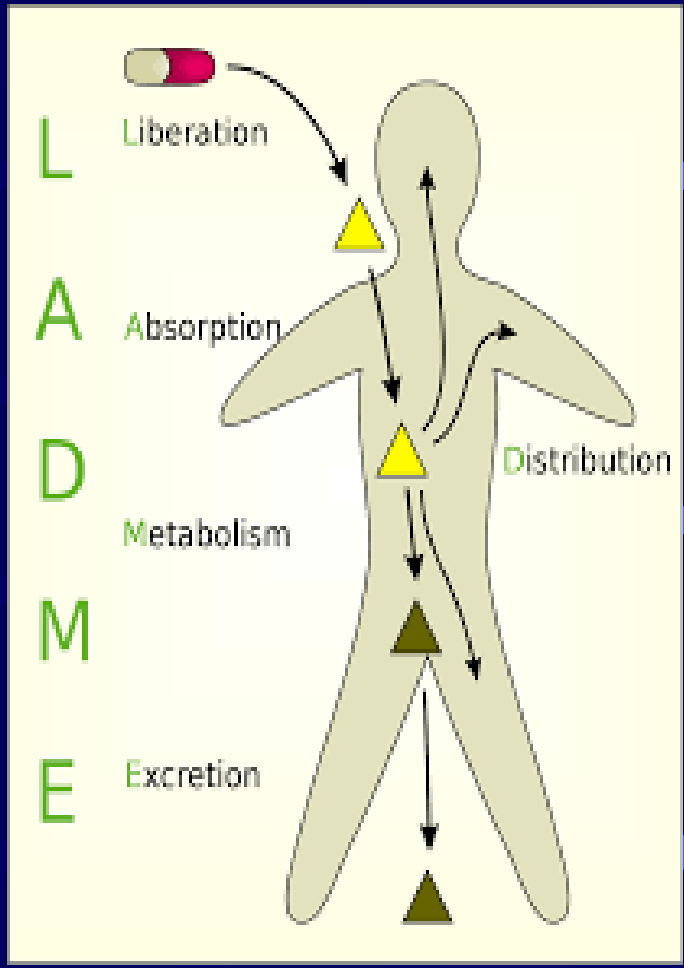
Pharmacokinetics - a field of pharmacology that describes changes in the concentration of a drug or its metabolites in the body over time.

The processes that pharmacokinetics deal with concern the fate of the drug in the organism and are described in the **LADME** system.

Pharmacokinetics considers these processes over time.

These processes are:

1. L - liberation
2. A - absorption
3. D - distribution
4. M - metabolism
5. E - excretion or elimination



In vivo and in vitro studies are the level of interpretation of pharmacokinetic processes (LADME).

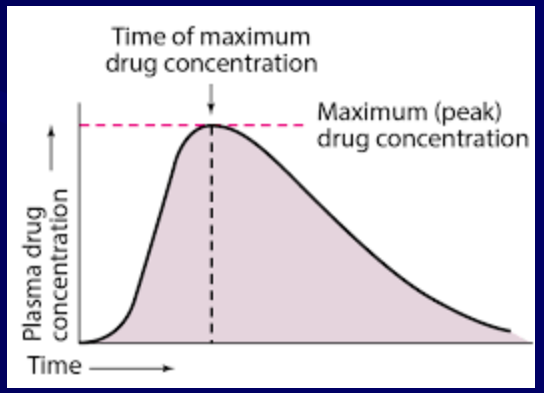
A complete pharmacokinetic description of a drug consists of a set of parameters that take into account the physiological and physicochemical processes the drug undergoes in its biophase over time, characterizing it in a mathematical and statistical manner.

The basic pharmacokinetic parameters are:

- constant rates of individual processes (absorption, elimination and others)
- bioavailability
- volume of distribution
- clearance
- biological half-life ($t_{0.5}$)
- average times of drug absorption and residence in the body
- maximum concentration and time of its occurrence
- area under the concentration-time curve (AUC)

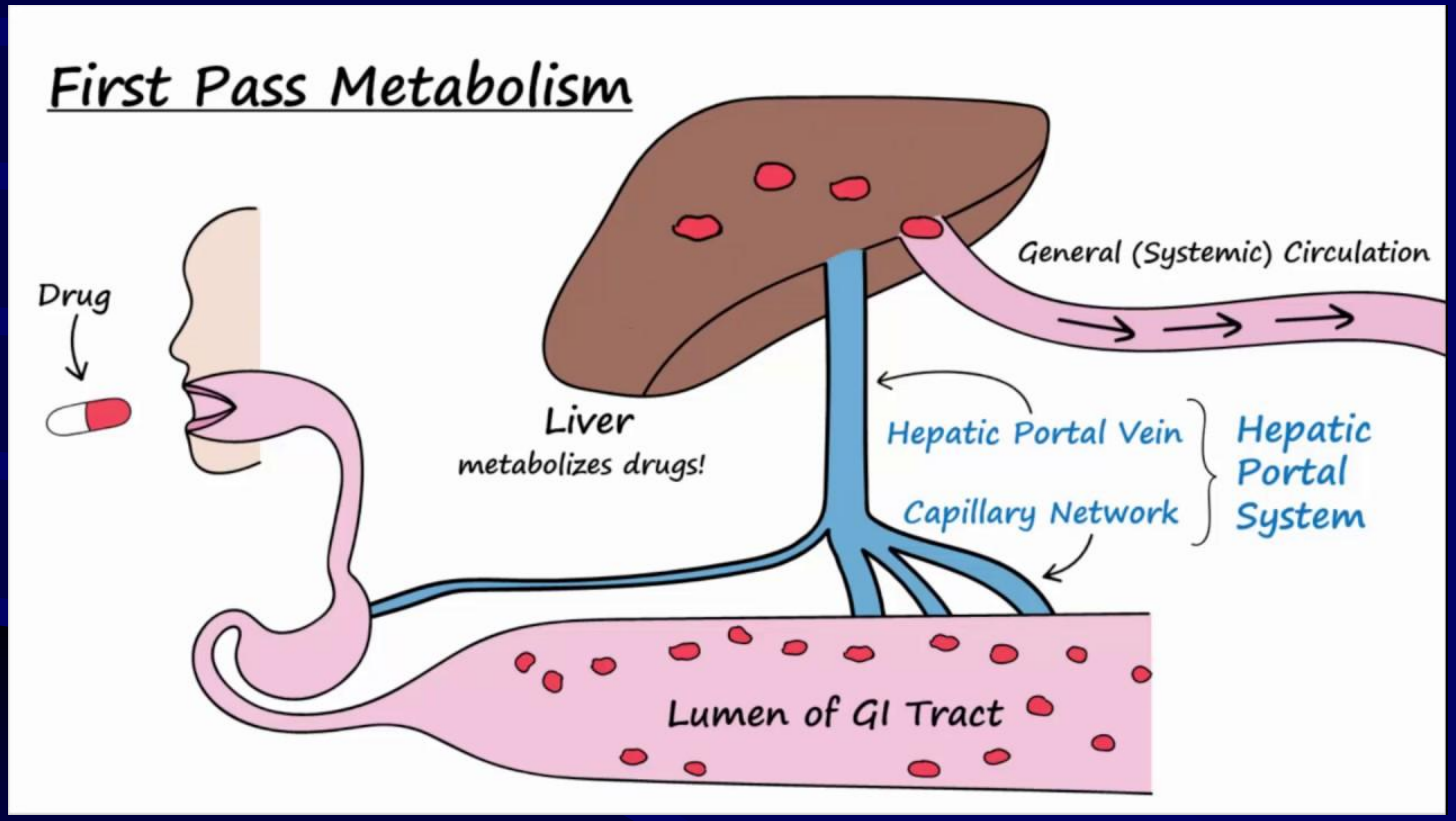
Cmax and Tmax

- Cmax is the maximum (or peak) serum concentration that a drug achieves after the drug has been administered and before the administration of a second dose
- The related pharmacokinetic parameter Tmax is the time at which the Cmax is observed



Bioavailability

- Bioavailability is a subcategory of absorption and is the fraction (%) of an administered drug that reaches the systemic circulation
- By definition, when a medication is administered intravenously, its bioavailability is 100%.
- However, when a medication is administered via routes other than intravenous, its bioavailability is generally lower than that of intravenous due to intestinal endothelium absorption and first-pass metabolism.


First Pass Metabolism
Drug
Liver
metabolizes drugs!
General (Systemic) Circulation
Hepatic Portal Vein
Capillary Network
Hepatic Portal System
Lumen of GI Tract

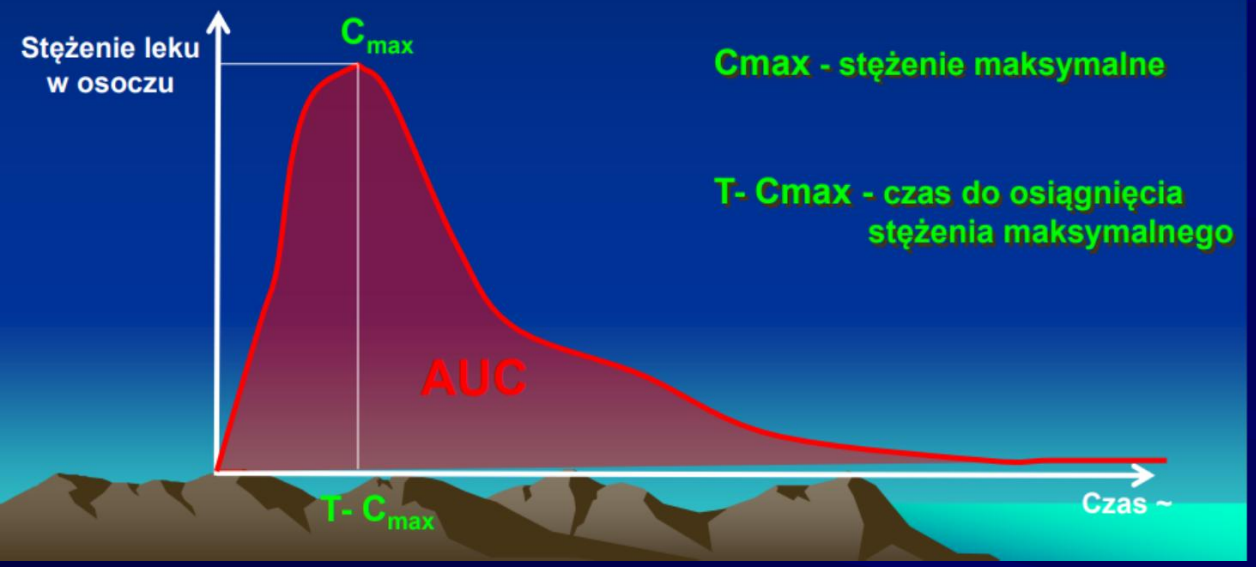
AUC

- Thereby, mathematically, bioavailability equals the ratio of comparing the area under the plasma drug concentration curve versus time (AUC) for the extravascular formulation to the AUC for the intravascular formulation.
- AUC is proportional to the dose that has entered the systemic circulation

- In order to determine bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs time plot for the drug after both intravenous (iv) and extravascular (non-intravenous, i.e., oral) administration.
- The bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous.
- The formula for calculating the bioavailability, F, of a drug administered orally (po) is given below (where D is dose administered).

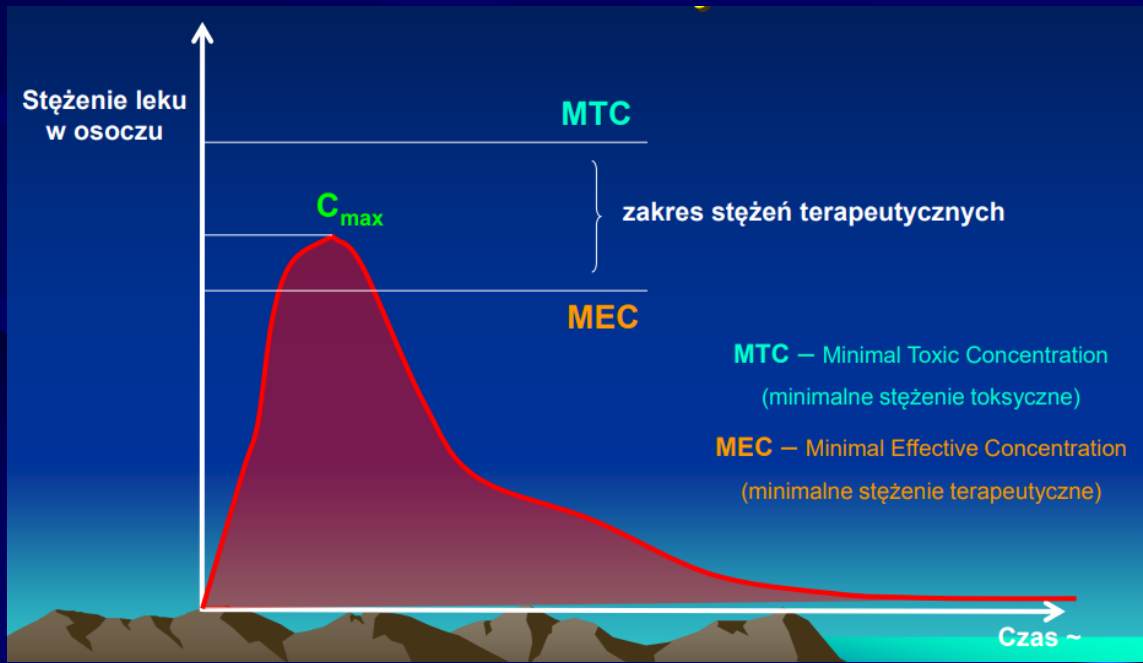
$$F = 100 \cdot \frac{AUC_{\mathrm{po}} \cdot D_{\mathrm{iv}}}{AUC_{\mathrm{iv}} \cdot D_{\mathrm{po}}}$$

AUC (Area under the Curve) - pole pod krzywą stężenia leku we krwi zależne od czasu



Cmax - stężenie maksymalne

T- Cmax - czas do osiągnięcia stężenia maksymalnego



MTC – Minimal Toxic Concentration
(minimalne stężenie toksyczne)

MEC – Minimal Effective Concentration
(minimalne stężenie terapeutyczne)

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Factors determining bioavailability:

- route of administration
- physicochemical properties of the preparation
- active substance released from the drug form
- the physiopathological state of the organism
- first pass effect
- drug or drug interactions and chyme at the site absorbed

Volume of distribution

(VD, also known as apparent volume of distribution, literally, volume of dilution)

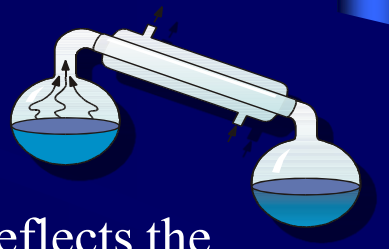
- is the theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma.

- In other words, it is the ratio of amount of drug in a body (dose) to concentration of the drug that is measured in blood, plasma, and un-bound in interstitial fluid.

- The VD of a drug represents the degree to which a drug is distributed in body tissue rather than the plasma.
- VD is directly proportional with the amount of drug distributed into tissue; a higher VD indicates a greater amount of tissue distribution.
- A VD greater than the total volume of body water (approximately 42 liters in humans) is possible, and would indicate that the drug is highly distributed into tissue.
- In other words, the volume of distribution is smaller in the drug staying in the plasma than that of a drug that is widely distributed in tissues.
- Volume of distribution may be increased by kidney failure (due to fluid retention) and liver failure (due to altered body fluid and plasma protein binding).
- Conversely it may be decreased in dehydration.

Clearance (purification factor)

the volume of plasma completely purified from a given substance per unit of time. It expresses the efficiency with which the plasma is purified of a given substance.



Usually, clearance is measured in L/h or mL/min.The quantity reflects the rate of drug elimination divided by plasma concentration.

Excretion, on the other hand, is a measurement of the amount of a substance removed from the body per unit time (e.g., mg/min, μg/min, etc.). While clearance and excretion of a substance are related, they are not the same thing.

- The drug can be removed by renal or hepatic excretion or both.
- the formula for clearance is:

- CLtotal = CL renal + CL nonrenal

- Mathematically, clearance is the product of the first-order elimination rate constant (k) and the apparent volume of distribution (Vd).
- Hence the clearance is the elimination rate constant – i.e. the fractional rate of drug loss – from the volume of distribution
- If a drug has a CL of 2 L/h, this tells you that 2 litres of the Vd is cleared of drug per hour.

Elimination state constant

- Determines how quickly a specific portion of a drug is cleared from the central compartment as a consequence of metabolism and excretion
- It is the fraction of the dose of the drug that is eliminated from the body per unit time
- It allows you to set the maintenance dose

$$K = \frac{Cl}{Vd}$$

Biological half-life, $t_{0.5}$, $t_{50\%}$

- it means the time during which the concentration of the drug in blood, serum or plasma decreases to half of its initial value, after the absorption and distribution phase is completed.
- It is expressed in hours.
- The higher the $t_{0.5}$ value, the more slowly the drug is cleared from the body.

Factors determining the biological period half-life:

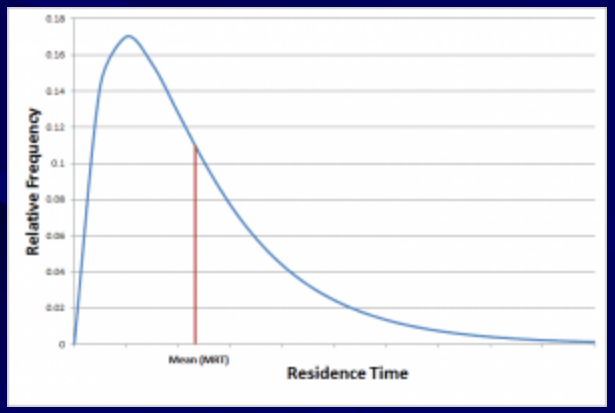
- genetic factors
- gender
- age
- capacity of the circulatory system, liver and kidneys
- the state of microsomal enzymes in the liver

- The biological half-life is most often analyzed in the elimination phase. This allows, among other things, to specify the dosage of the drug. The half-life value can be calculated for any process that can be characterized by a rate constant (distribution, absorption).

- It allows you to define the dosing intervals for drugs

The mean residence time (MRT)

- The mean residence time of a drug in the body is one of the basic parameters illustrating the kinetics of the elimination of substances from the body.



- The knowledge of pharmacokinetics allows for individual pharmacotherapy of the patient (monitoring of the drug concentration in the blood) combined with the observation of the patient's clinical condition.
- This is especially important in relation to drugs with a narrow therapeutic index, when the difference between the therapeutic dose and the toxic dose is small.
- In such cases, pharmacokinetic tools allow, based on two or more measurements, to calculate a dose that will be therapeutic and non-toxic for a given patient.

THANK YOU FOR YOUR ATTENTION