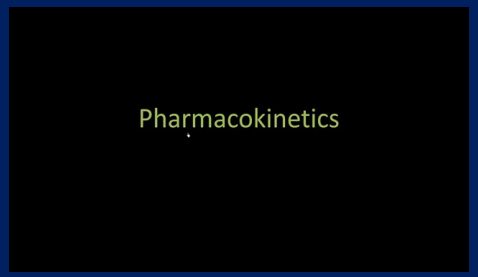
C.10.

Elements of theoretical pharmacokinetics

- Pharmacokinetics modelling



Pharmacokinetics

provide information:

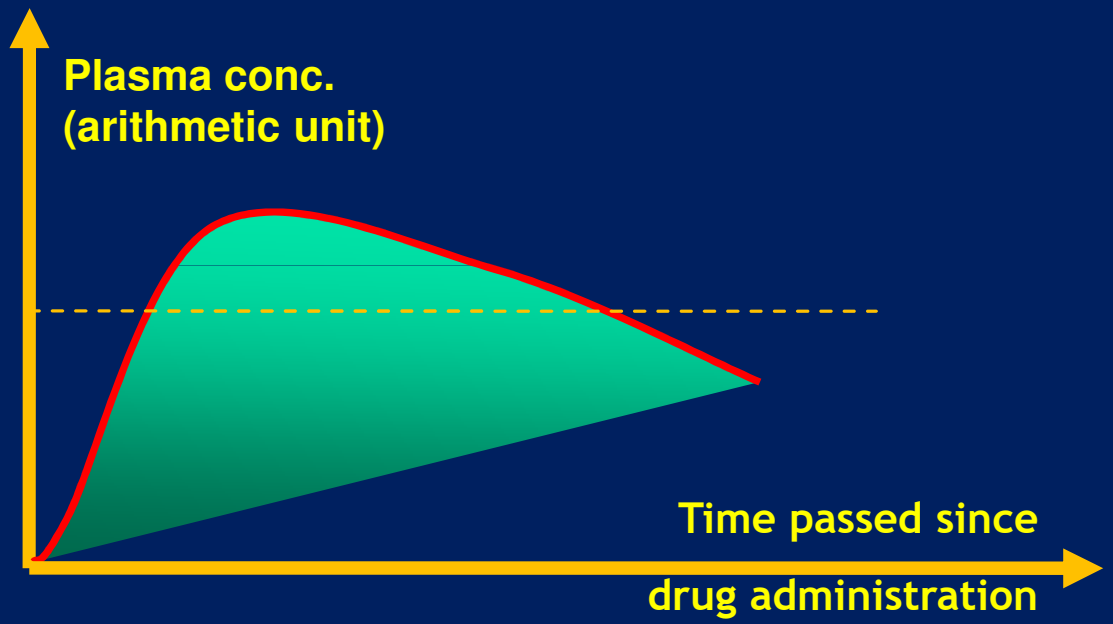
- about the "fate" of substances administered externally to a living organism and
- explores the interactions of absorption, distribution, metabolism and excretion by analyzing the relationships between:
- plasma concentration and
- time elapsed after administration

Studies so far have shown that it is possible to know:

- The plasma concentration at which the effect becomes apparent;
- The correlation between the intensity of the effect and plasma concentration.
- The correlation between the effect duration and the period when plasma exceeds a certain value, and
- The effect disappears when plasma concentration drops under this value.

The situation applies to most drugs that:

- act instantaneously,
- do not require metabolizing into an active form
- have a reversible coupling with receptors and
- do not have an irreversible effect.



Hypothetical representation of a plasma concentration-time curve
(Brander, 1991)

- **Kinetics** redundancy

Absorption

Is the unique factor that determines the initial growth of drug plasma concentration.

Distribution, metabolization and excretion

will remove the free pharmacon from plasma resulting in a decrease of its concentration.

Instead of identifying and measuring the individual contribution of these three processes mentioned above, an act of kinetic simplification would be to unite them, in a process called redundancy.

It defines the kinetic disposition of a drug by calculating the equation that fits the plasma concentration-duration curve.

Generating curves (while searching the best equation to fit the gross data) is known as: mathematical modeling.

Drug concentration is essential for its efficiency in the place where the action between its molecules and the biological partner of reaction unfolds.

Depending on the action mechanism, this reaction can occur:

- intracellularly,
- extracellularly,
- in the blood,
- in the CSF,
- in the urine etc.

The obtained values provide information about:

- the elimination rate and
- the apparent volume of dissemination

- The monocompartmental open model

The simplest model is seen as:

a simple fluid space where the pharmacon is administered and where it will diffuse until it reaches a state of equilibrium.

The term "open" describes the continuing loss of drug from the compartment, and represents the organism's "opening", meaning that the consequences associated with drug loss during metabolization and excretion, will determine the uncoupling from the receptor and therefore, ending the drug's action.

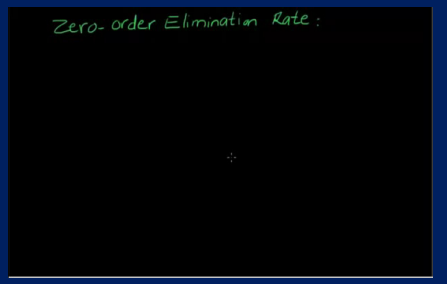
The drug concentration in the biophase stops increasing when:

- the addition rate through absorption of the pharmacon in the biophase is exceeded by the removal rate through the elimination process.

Therefore:

- the intensity of the response depends on the quantity of the pharmacon present on receptors.
- the duration of the response depends on the elimination kinetics of the uncoupled fraction.

After studying the drug's plasma concentration, it can be demonstrated that in some cases, the rate of drug loss from plasma, after reaching the dissemination equilibrium, is constant in terms of mass unit / time unit.



In these conditions, it can be said that:

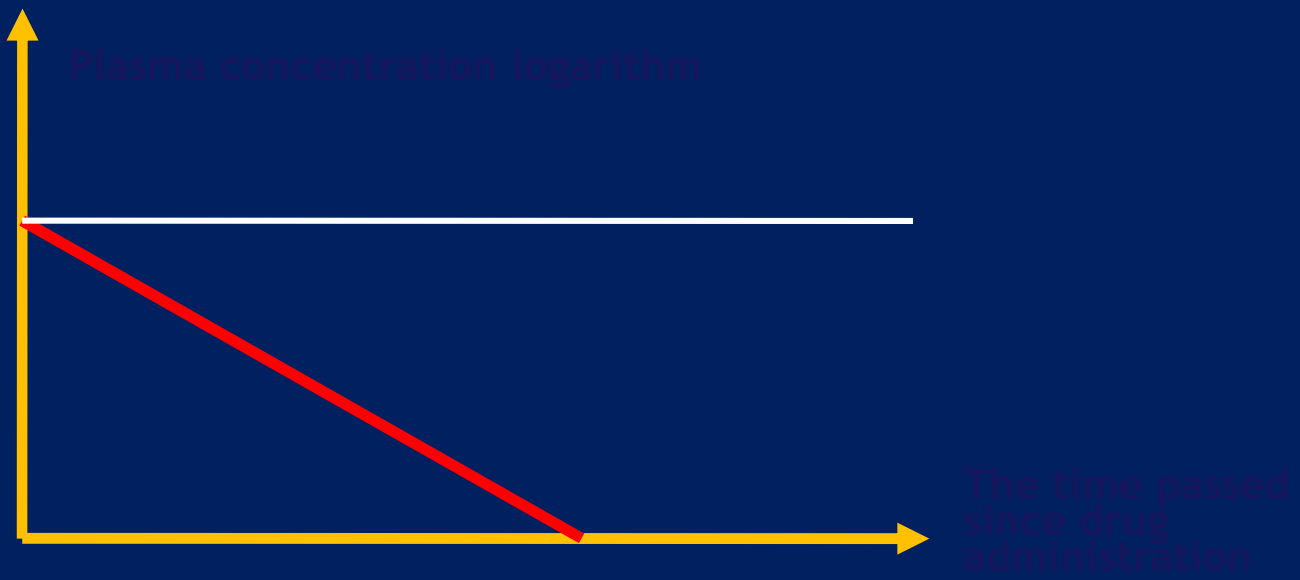
"the plasma concentration per unit of time, is represented by a straight line".

More often, the decrease of plasma concentration follows the first order kinetics, where "a constant fraction of the drug is eliminated per unit of time".

Such a relationship, arithmetically represented, would offer an exponential curve that could turn into a straight line if the representation would be semilogarithmic.

The monoexponential process can be defined by *its constant rate* that expresses *the fraction's modification per time unit* or by the *half-life (t1/2),* that means the time it takes for the blood plasma concentration of a substance to halve its steady state.

Both values are independent from plasma concentration, meaning that they are constant no matter the concentration.



Continuous i.v. Injection
The organism behaves like an open monocompartmental system
(Kuschinsky, 1989)

- The bicompartmental model

This model consists of two areas:

- the plasmatic area (PS) and
- the extracellular area (ECS),

whose separation barrier is easily crossed by the pharmacon.

The pharmacon reaches:

1. the central compartment, and from here,
2. the second compartment (SEC).

This model describes the behavior of a pharmacon that

- disseminates extracellularly after entering the blood,
- and concomitantly,
- is eliminated through renal excretion.

The size of the two areas represent in adults:

- first area, approx. 4% (PS) and
- second area, 16% (ECS) of total body weight,

therefore, a ¼ ratio exists between the two areas.

There are two known outcomes:

a). the drug passes into the ECS and back *very fast* regarding the elimination process (k12 = k21 > k3) and

b) the elimination speed is in *the same domain with the diffusion speed* from the central space into the peripheral space (k12 = k21 ≈ k3).

The curves from the next figure represent:

The a. variant:

after injecting a dose of 100mg/kgbw into the bloodstream, the pharmacon *diffuses very rapidly* in the two compartments and its dissemination will end after approx. 5 minutes.

If the elimination does not take place (k3=0), an equilibrium will be established (discontinued horizontal line); the concentration should reach 0,5mg/ml in both compartments, the total amount of pharmacon being divided into:

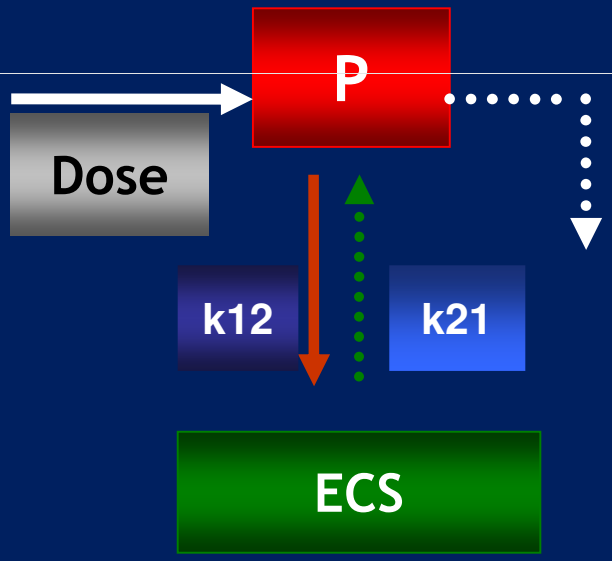
- 80% în ECS and
- 20% în PS.

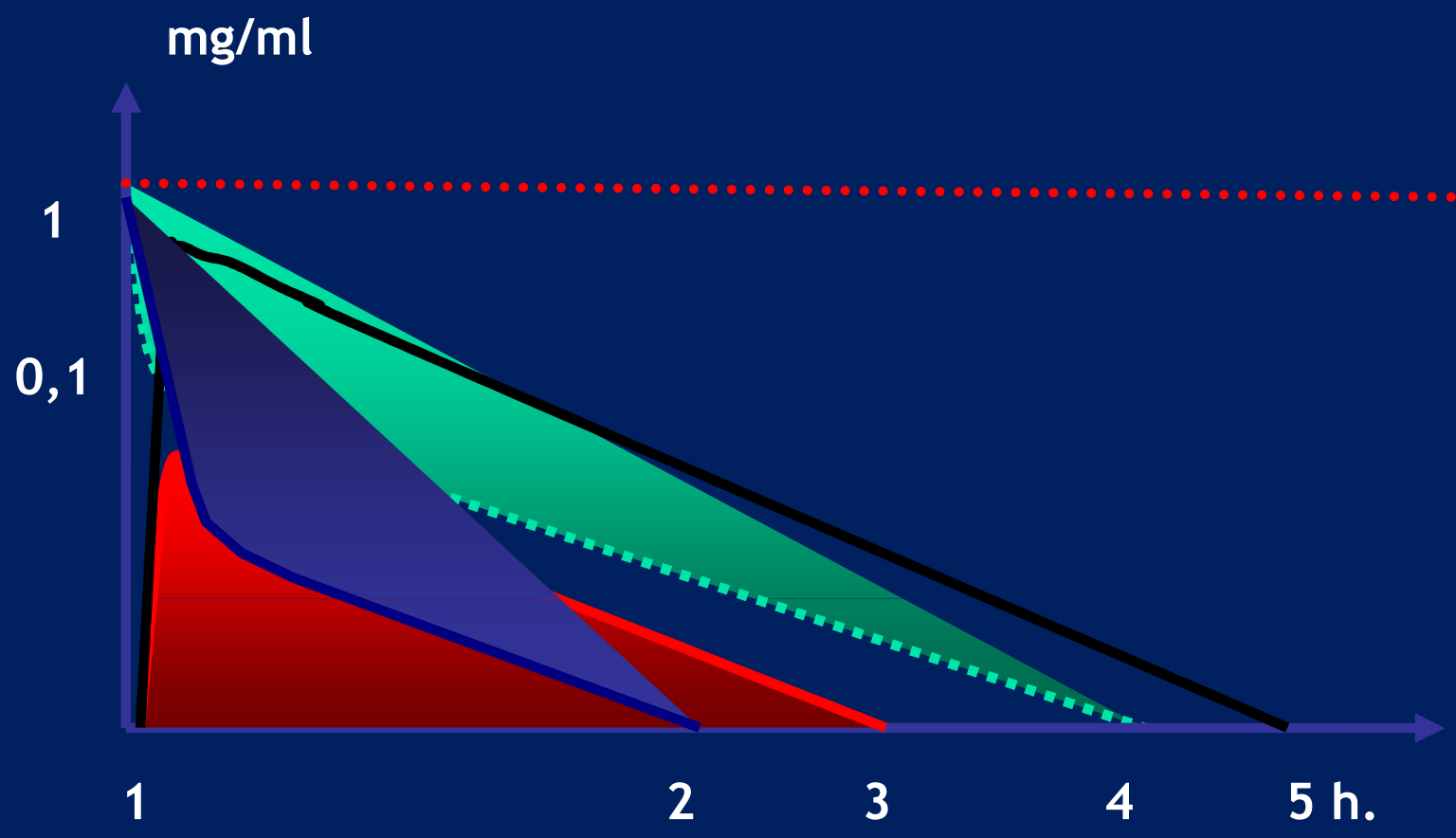
The half-life of the blood level is a complex quantity called β value.

The retropolation of the β phase on the ordinate shows that the concentration level of the plasmatic compartment is much lower than it should be for the administered dose.

Therefore, *the apparent monocompartmental system is mentioned*.

In addition, the figure also represents the concentration variation in the ECS (superior continuous curve), that in β phase evolves parallel with the plasma concentration, but has a higher level.


P
Dose
k12
k21
ECS



Evolution of the plasma concentration(P) into the extracellular space (ECS) after iv. administration of 100 mg subst. / kgbw (bicompartmental model) (Kuschinsky, 1989)

The b. variant

The distribution process between the two compartments is proportionally reduced, and the renal process is relatively fast.

As it is shown in the figure, the primary dissemination phase is marked by a sharp drop of the blood level, only when the concentration reaches approx. 0.04 mg/ml the logarithmic-liniar terminal phase begins, and its retropolation on the ordinate renders the concentration of 0.08 mg/ml.

From here, a fictitious value is frequently calculated :

the apparent volume of distribution (dissemination), that can emerge from the relationship:

At a dose of 100 mg/kg, which, in the case of a uniform distribution in the body, would have to realize the concentration of 0.1mg pharmacon /ml, however, at time 0, through retropolation, a concentration of 0.08 mg/ml is obtained, therefore the apparent distribution volume will be 1.25 l / kg.

- **The tricompartmental model**

Because many pharmacons disseminate not only into the PS and the ECS, but also enter into the intracellular space (ICS), means that they bind to the cellular membranes.

Their kinetics can be described only using a tricompartmental system.

Usually, the process of analysis of the drug distribution into the body is based, in principle, on the establishment of plasma concentrations and assigning these values to the other compartments.

If a pharmacon accumulates or binds to a specific location in the body,

▼▼▼

A very important biological principle, is to consider the body compartments as sizes given from the beginning, because they are known and can be established independently.

The pharmacon concentration in these spaces should be considered as a variable.

In this way, we can calculate the amount of pharmacon from each compartment.

For example:

The administered dose is shown in a proportion of 100%, in addition to the amount of plasma (4% of body weight) and ECS (16% of body weight) it is rendered also, the quantity of substance excreted by the kidneys.

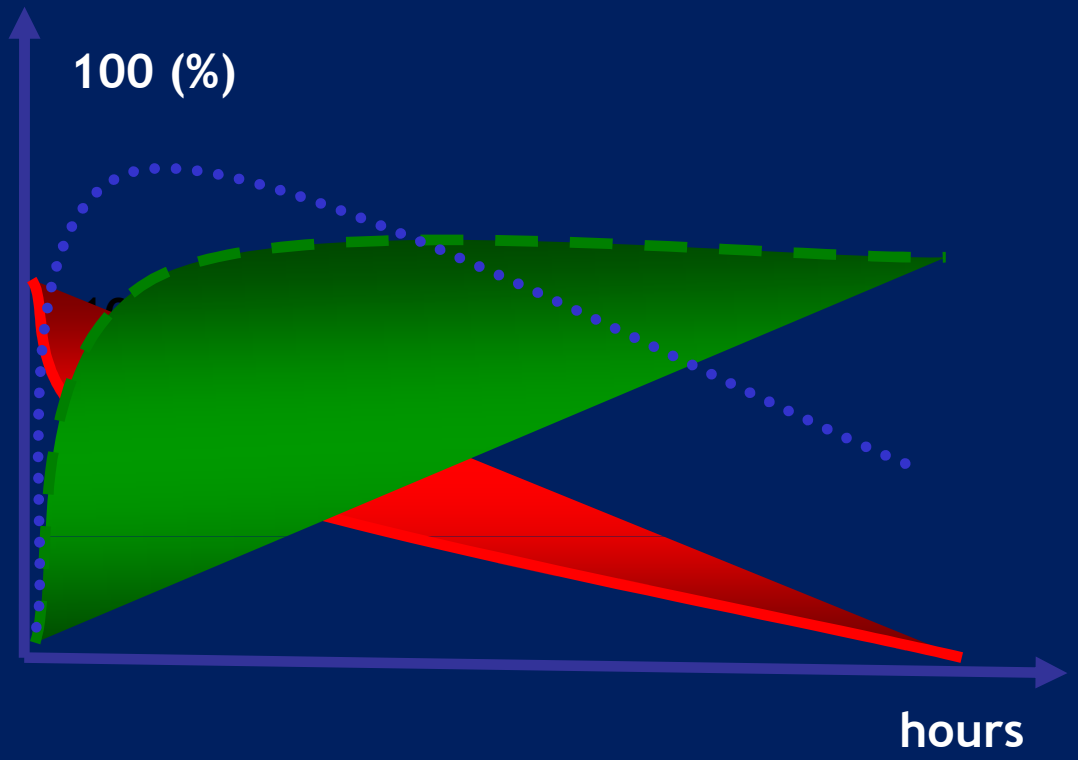
Immediately after the injection, the pharmacon leaves quickly the PS, after approx. 10 minutes, 40% of the substance reaches the ECS, 20% is eliminated by the kidneys and after approx. 20 minutes, the ECS contains 50% of the dose and 30% has been eliminated.

After 40 minutes the distribution phase is finished.

In the PS there is only 10% of the dose, but in the ECS, 50% of the dose can be found.

During the terminal phase, the quantity of substance in the ECS is 6 times higher than the one from PS.

When taking into account the sizes of the compartments, the concentration in the ECS, from a biological point of view, is 1,5 times higher.



The percentage of the temporal distribution of a drug after iv administration into the plasma (continuous line) ECS (dotted line) and urine (dashed line. The amount injected was immediately available in a percentage of 100%.
On the ordinate there are represented the logarithmic units, and on the abscissa the hours. (Kuschinsky).

In this case, such an example is imagined:

The quantitative influence of the ICS (of high capacity) is obvious, because it represents 50% of the body weight, compared with 16% of ECS and 4% of PS.

In the case of a proportional distribution of a pharmacon, it is expected to be found approx. 5% of the administered dose in the PS (if the elimination does not occur).

it is apparent that:

- within one hour after the administration, the quantity of pharmacon from the PS has decreased to 3%;
- in the ECS, during the period of time between the 5th minute and the 10th minute, a maximum value is attained (approx. 35% of dose);
- the quantity of substances from the ECS increases relatively fast during the distribution period and reaches a maximum value, after approx. 30 minutes.
- At that moment 50% of the administered dose is in ECS.

The dynamics of the concentration, that results in SP and in the second compartment after repeated administration is represented in the following figure.

Meanwhile, the blood picture does not render, almost at all, the accumulation phenomenon, in the tissular compartment the concentration increases abruptly.

This kinetic behaviour of a pharmacon (with increasing quantity in the neighboring compartment, in conditions of fast blood elimination) is important for the practical therapy, because the compartment where the therapeutic effect is taking place, is almost always a compartment that is adjoined to blood.

a). The quantitative determination of substances in blood , in these conditions, does not provide information about the concentration of the pharmacon and about the temporal modifications from the place of action.

b). The half-life of PS does not reflect changes in the concentration at the action site.

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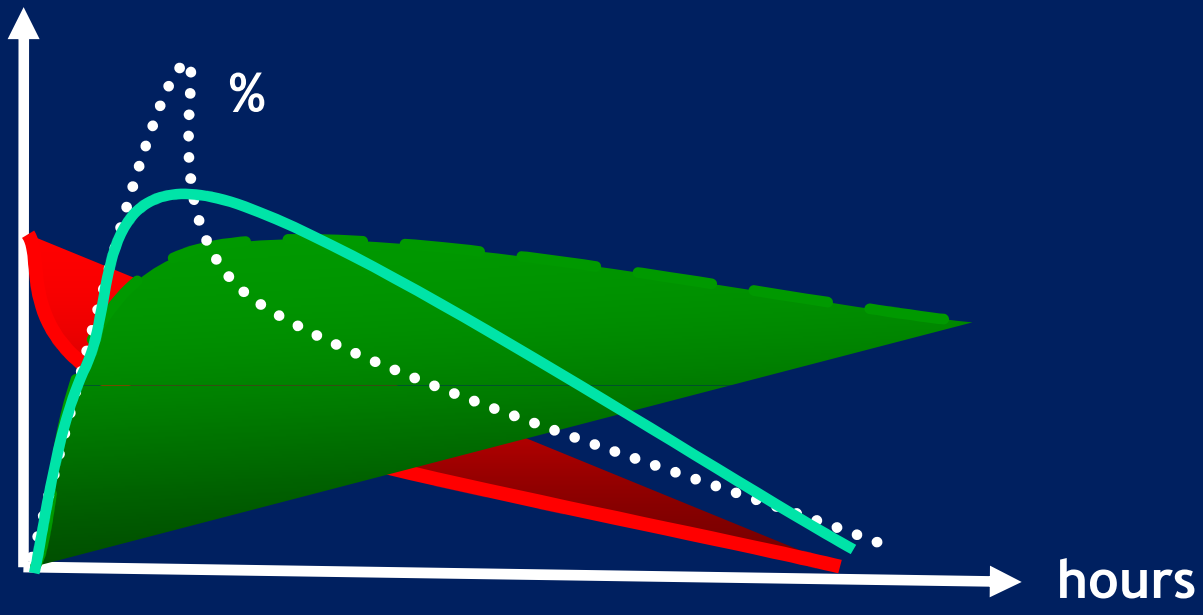


The percentage of temporal distribution after iv administration of a drug, in plasma (thick solid line), ECS (dotted line), ICS (thin solid line), urine (dashed line) (tricompartmental model) (Kuschinsky, 1989).

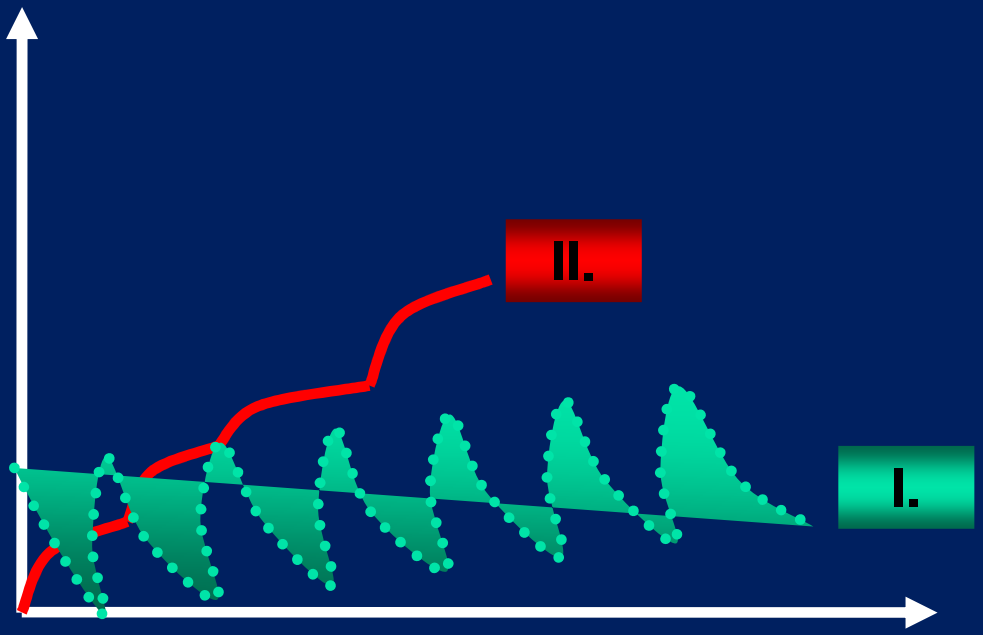
This assumption is demonstrated by an example:
Thiopental, is lipid-soluble and accumulates in fat tissue.
Three hours after administration it is still found (70%) in the fat tissue, although the blood level has dropped below the level that obtains the effect, and the narcotic effect disappeared.
The concentration in the cerebral compartment is closer to the evolution of blood concentration rather than the concentration of fatty tissue.
The concentration from the fatty tissue remains increased for a long time, compared with the blood concentration.

Therefore, in the case of a re-administration, this fact is easy to observe, because Thiopental reaches a presaturated deposit tissue.

The result of this fact is a persistent and a higher blood level, and the risk of poisoning when re-administering a higher dose.

Due to their physico-chemical characteristics, drugs are hydrophobic, and at a physiological pH, they are mostly under the form of free bases, and in normal blood conditions, they can achieve very high tissue levels that cannot be determined just by the simple analysis of blood level.

Starting from this perspective, several conclusions can be drawn regarding the therapeutic approach mode of a substance, especially in the case of repeated administrations.



Increasing drug quantity is the consequence of repeated iv administrations.
The drug has high affinity for the tissular compartment (k12> k21).
When examining the blood picture (I) a barely detectable accumulation can be observed. In the tissular compartment (II) the drug's level increases, leading to toxic threshold only after a few administrations .

The evolution of terminal phase provides information about the biological half-life of a substance.

Establishing the terminal phase is of importance, when:

a) The control points are situated in the multiple time interval of the biologic half-life time;

b) Only the pharmacon is analyzed, and not its metabolites (this possibility of error occurs when a radiolabeled pharmacon is used, or when an immunological procedure is applied).

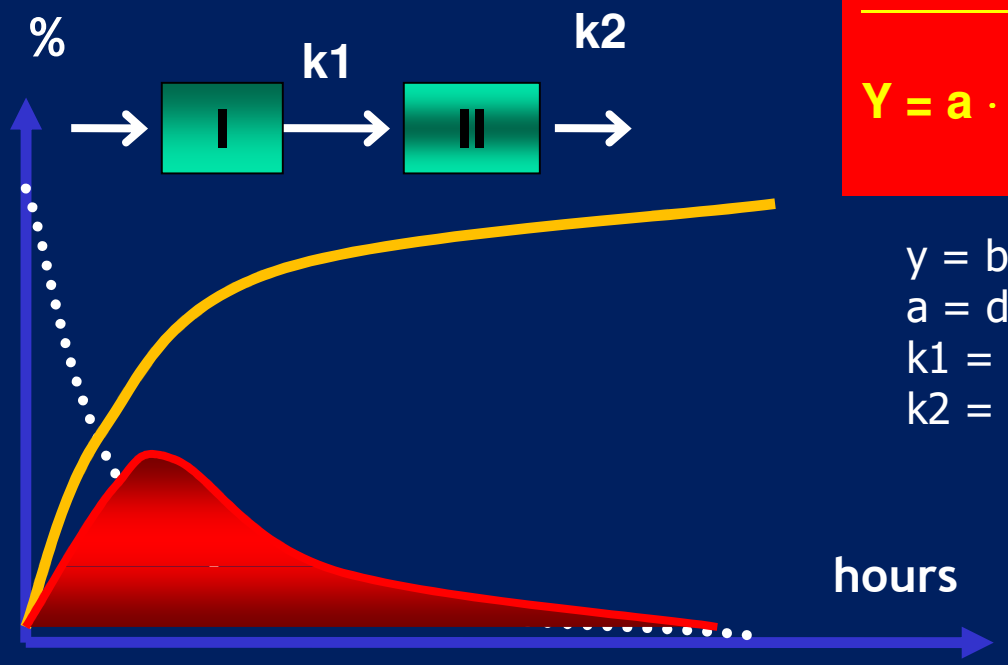
c) In the case of some enantiomers with different effectiveness not only the racemic behavior is established.

- Bateman's function

A common method used in drug therapy, consists of the administration of pharmacons at regular intervals, over a long period of time.

Mathematical

We are dealing with the "*cumulative function of Bateman*" (basically, the new administered dose is added to the quantity of drug that can still be found in the body).



The Bateman's function

$$Y = a \cdot \frac{k1}{k1 - k2} \cdot (ek2t - ek1t)$$

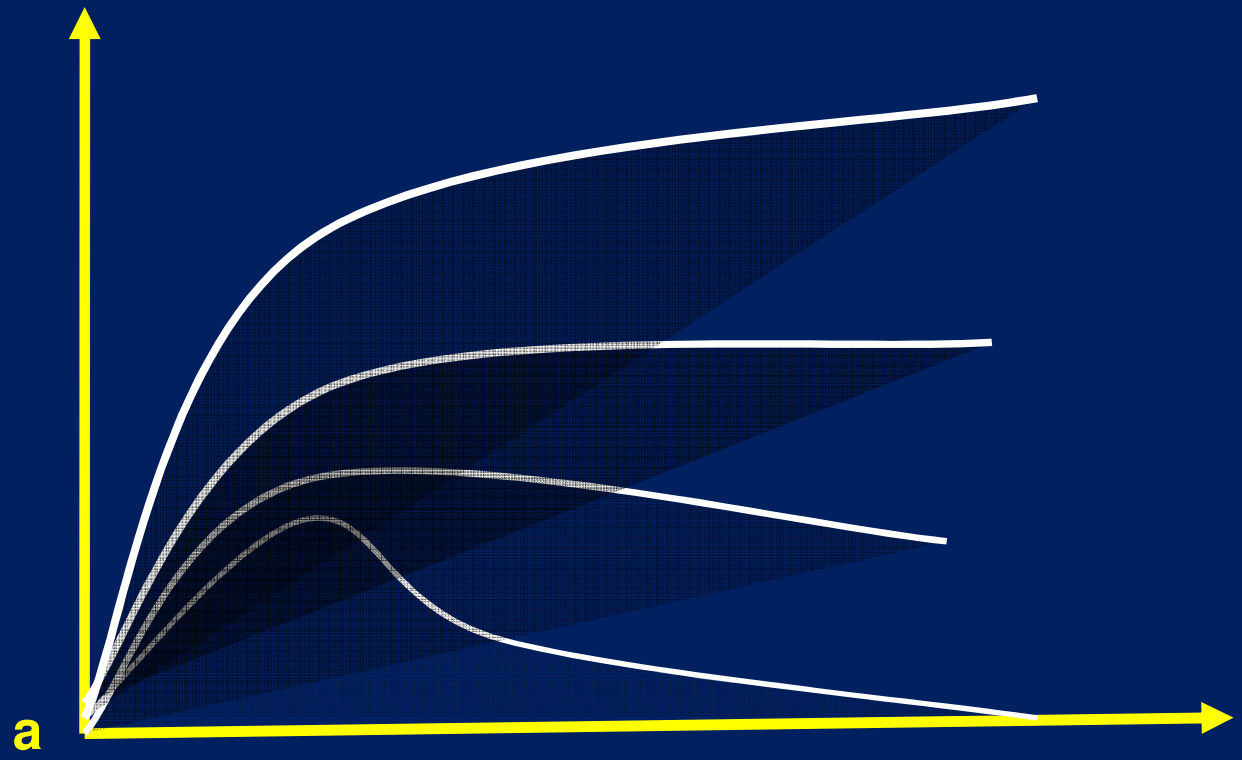
y = blood picture at time t;
a = dose expressed in concentration;
k1 = the invasion constant;
k2 = the evasion constant.

The evolution of the blood picture after administration of a drug in a compartment situated in the vicinity of the vascular compartment (I) (gastrointestinal tract, intramuscular deposit), from where, by invasion (resorption) it reaches the bloodstream (II) where it will be removed.
The black curves represent the invasion process, respectively evasion, and the red line shows the blood picture fluctuation.

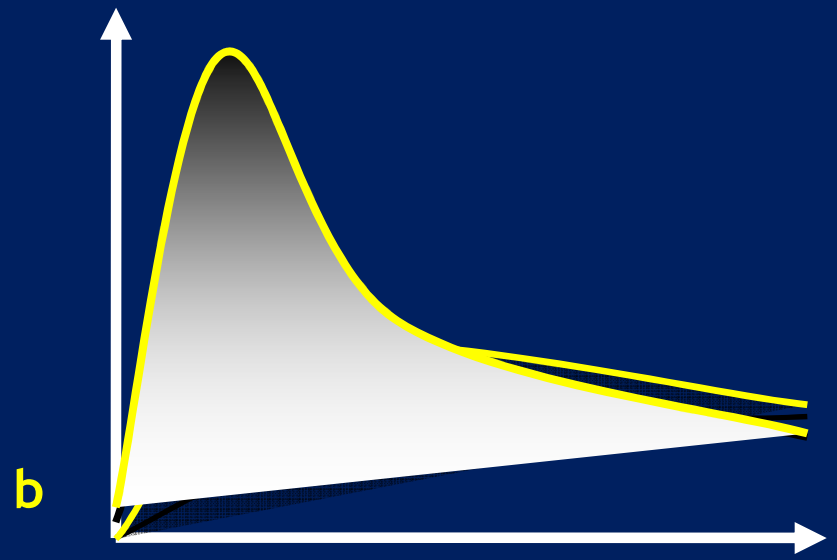
- The intestinal absorption is characterized by the absorption constant (invasion), and
- The elimination from the blood is characterized by the elimination constant (evasion), because both processes are irreversible.

This function can be applied also if the administration is not oral, but under the form of an i.m. or s.c. deposit.

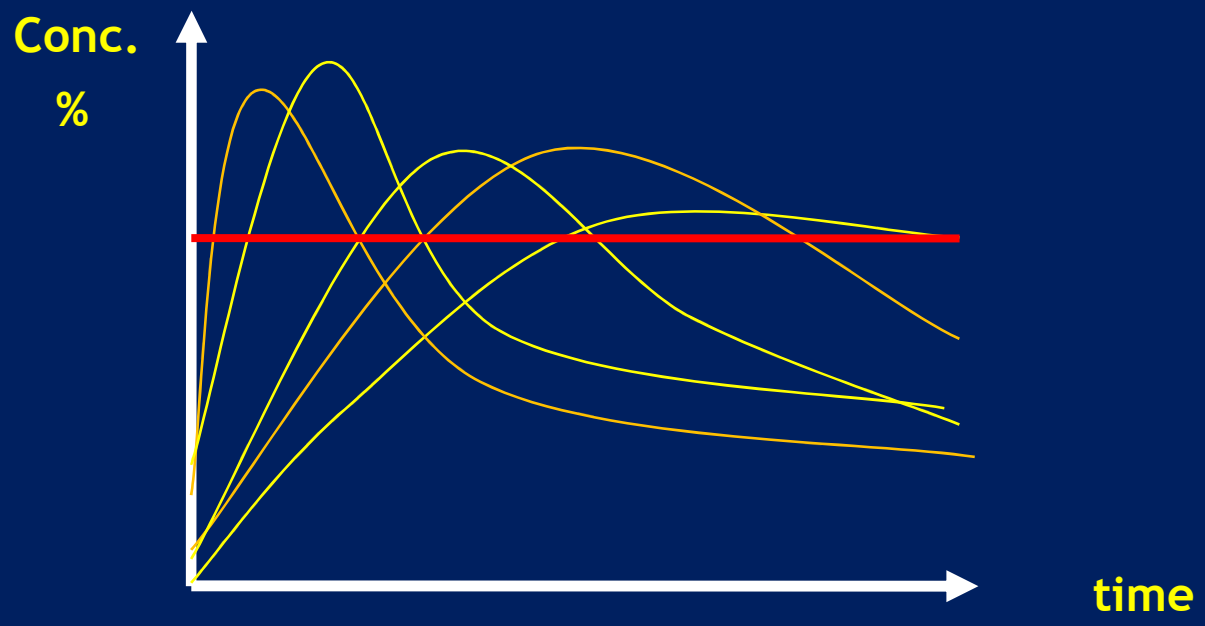
- The absorption and elimination constants (invasion and evasion)



The influence of the invasion and evasion constants on the blood picture.



If the administered dose and the invasion constant are kept constant, and the evasion constant varies systematically, then will result curves as the ones shown in figure a .
On the contrary, if the dose and the constant elimination are constant, and constant invasion varies systematically, then we will obtain the curves from figure b. (Kuschinsky, 1989).



Evolution of blood picture (Bateman's function). When the invasion constants are different, but the chosen doses ensure the attainment of the same maximum blood levels. Attention should be paid to the different ways that the blood picture evolves (duration) in each case. (Kuschinsky, 1989)

- The minimum blood level

Therapeutical

it is necessary to exceed a minimum blood level of the drug for a certain period of time.

When the absorption rate is too low or the elimination speed is too high, in order to achieve the necessary blood level, the third variable, meaning the dose, must be increased.

and in the case of the cumulative function of Bateman,

- the dose,
- the absorption constant and
- the elimination constant
- represent known sizes;

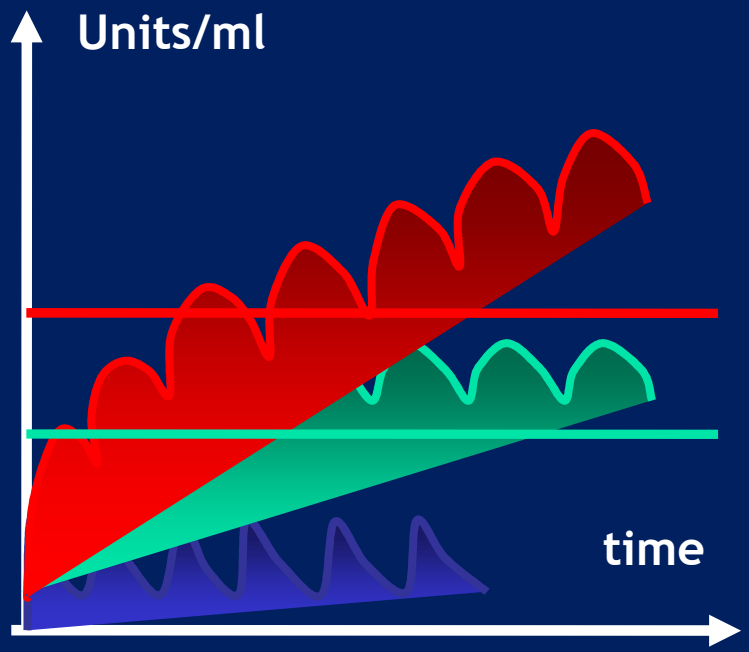
the new variable that occurs is:

the size interval τ, namely, frequent administrations.

In order to demonstrate the evolution of blood levels over a long period of administration, using different elimination constants, the following example was created:

Three pharmacons differ only by:

- ► the elimination constant,
- ► they produce the same blood level and
- ►are administered in the same dose.



The variation of the blood picture when administering three drugs daily, in a compartment adjacent to the vascular space. The three substances differ only by different evasion constants. From a mathematical point of view, *the cumulative function of Bateman*, where, (*the administration frequency*) interferes as a new variable. The doses, the constants of invasion and the intervals between administrations (in days) are the same for all three substances, but the evasion constants differ : 0,2 (bottom curve); 0,02 (middle curve) 0,01min-1 (superior curve). (Kuschinsky, 1989).

- The disruption of a drug administration

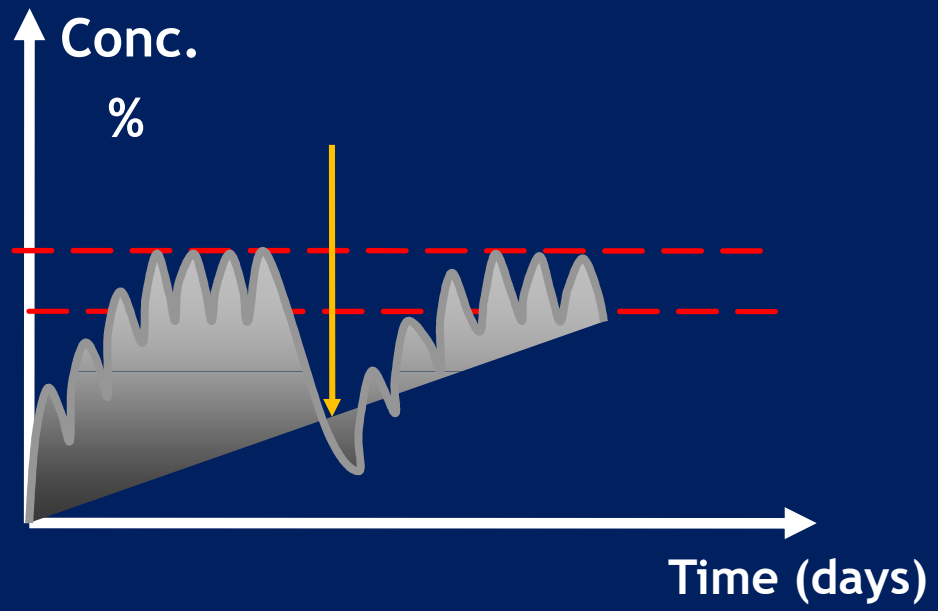
In most cases,

the goal of a lasting therapy is to achieve a "constant" blood picture by choosing an optimal *pro dosis* value and an interval size.

Example.

On the 8th and 9th day, the treatment realization is omitted.

In these conditions, the blood level drops drastically, because the elimination constant is determinant.



The influence of a disruption of the administration on the "average blood picture" in case of a prolonged therapy (cronic).

Omitting two administrations leads to a delay, bigger than two days in the restoration of the efficient blood picture.

After the resumption of the administration, it takes another 4 days until an equilibrium is reached again.

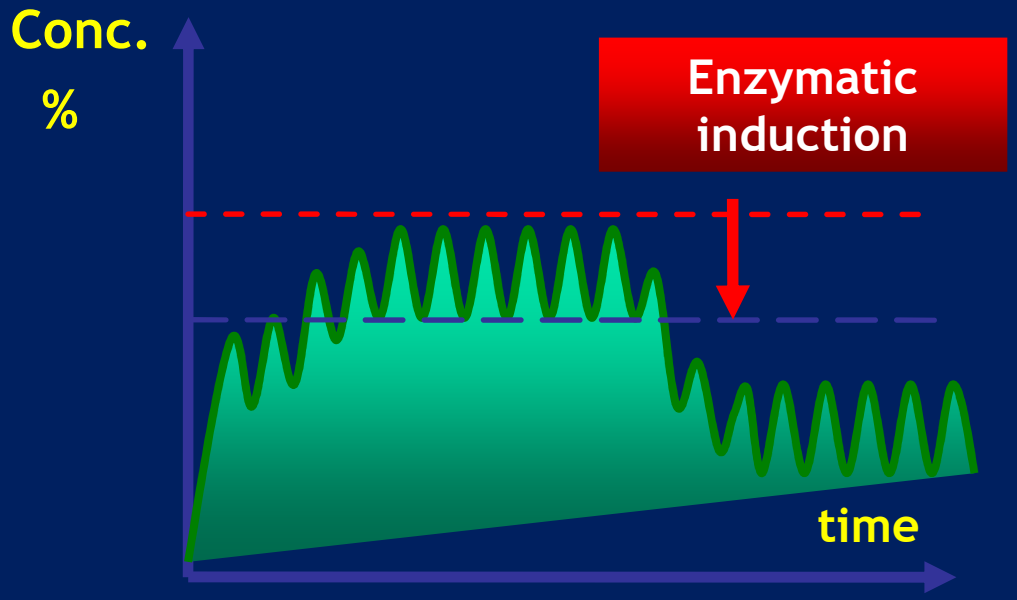
Therefore: the **2 day interruption** translates to a total loss of approximately 6 days under the therapeutic necessary level!

- Enzyme induction and blood level

For example:

In one case an optimal blood level is obtained (but from the 12th day of treatment, the patient is given a second drug, which causes an enzyme induction in the liver.

Corresponding to this administration, the elimination rate of the first pharmacon will expand.



The influence of the increased rate of evasion over the medium blood picture in case of chronic therapy. The decrease of blood levels is due to the enzyme induction caused by another drug. The increased elimination rate causes the decrease of the blood level and the establishment of a new equilibrium level, but situated under the therapeutic one. (Kuschinsky, 1989).

- The parameters of pharmacokinetic quantification

The pharmacokinetic evaluation of the quantitative consequences determined by the absorption process and the elimination of drugs, is obtained by viewing the body as a "machine that works mechanically".

This machine is seen as performing two actions after the administered drug dose:

- first *dilute* the drug and

- then *remove it*.

The drug concentration at any moment, is the measure of the diluted fraction remaining at that time from the administered drug.

The rate at which the concentration decreases over time is the measure of the “machine's” capacity to eliminate the drug.

Furthermore, they are independent of the size of the dose until one of the involved mechanisms becomes saturated. (ex: the coupling capacity and the degradation paths).

After the i.v. administration, the dilution includes:
- the pharmacon mixes with the blood,
- the pharmacon exits the vascular space into the distribution volume and
- the loss of free drug to the receptors by coupling, lipid solubilization and ionic capture.

Determination of the dilution capacity and the speed elimination constant can be made experimentally by administering a single dose i.v.

The correlation

Between the administration of a drug and the pharmacological or toxicological final effect is determined by many factors.

The transformation into biological effects is closely related with the coupling of the pharmacon on specific or nonspecific sites (*transformation kinetics*).

Transforming receptors' occupancy in effect is probably directly proportional only in exceptional cases, in the rest of the cases it submits to complicated functions.

Hence, it results that there are different growth rates of the dose-effect curves, that represent the dependence of the effect on concentration.

The transformation can take place quickly and directly (ex: increasing the ionic permeability of the terminal plate membrane after binding acetylcholine to acetylcholine receptors), but it requires a sequence of processes (or may even be a slow process).

Examples in this regard are:

- the effects of hormones with a steroid structure on the synthesis of proteins or
- the inhibition of blood clotting factors by coumarin.

In these cases, the transformation occurs much slower compared to the two previous kinetic processes.

Factors and processes involved in the onset of the activity of a drug

Pharmacokinetics	**Dose; administration method ; galenic disponibility; invasion into the venous system; presystemic elimination (liver, lung) the great arterial circulation volume, distribution, elimination (metabolization and excretion) concentration into biophase;**
Receptor kinetics	**Biophase: concentration, the receptors affinity, binding site;**
The transformation kinetics	**coupling transformation of drugs in pharmacologic or toxic effect.**

Generally,

the drug gets distributed in the body and reaches the target organs, through the blood pathway.

There are two main types of administration:

- oral and
- parenteral.

After *oral* administration, in general, the pharmacon gets reabsorbed by the gastrointestinal mucosa.

Blood drainage

It is done through the portal vein that develops a new capillary territory in the liver, leading to the decrease of the flow rate in this zone, implying a prolonged contact of the liver cells with the blood.

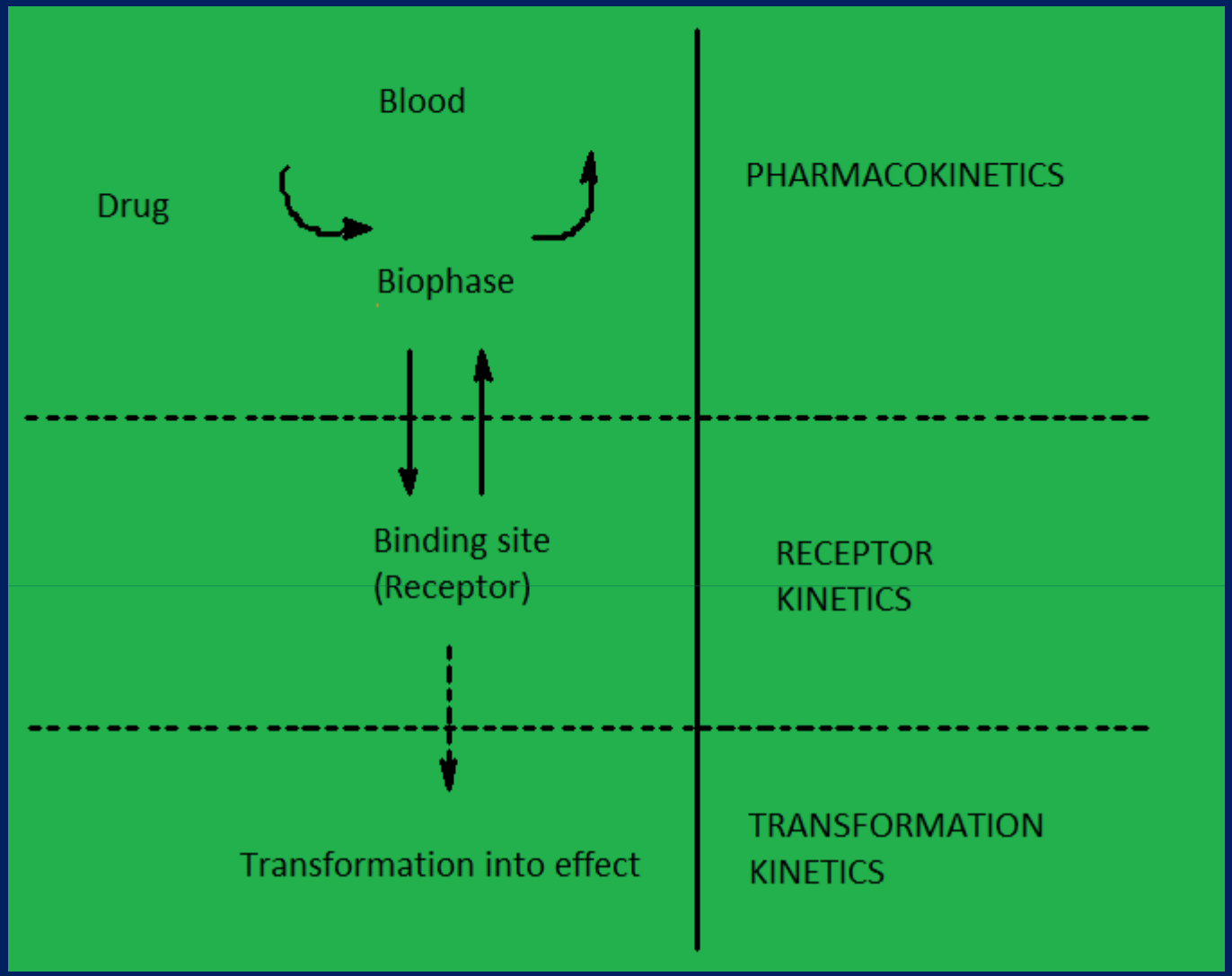
Therefore, an intensive exchange of substances can be possible.

Some part of the quantity of the reabsorbed substance can thus be captured = lost at the first hepatic passage or "first pass efect".

The fact that a part of the pharmacon's quantity that is reabsorbed at an intestinal level is retained in the lung and liver, before reaching the big circulation, can be called, in conclusion, *presystemic elimination*.

From here, the blood passes the right heart and then into the lung, where due to capilarization an intensive contact with the tissue cells takes place.

Here, a part of the substance absorbed from the gastrointestinal system can remain, because the lung has a high coupling capacity for amphiphilic and lipophilic substances.



Representation of the major kinetic processes that can influence the speed of installation of the pharmacologic effect of a drug product.

When administering *intravenous injections*, the pharmacon goes straight into the blood, but must pass the lung barrier before reaching the big circulation.

When rapidly administering a drug, by iv injection, the lung can act as a buffer, in order to protect the following organs from excessive concentrations, such as the myocardium, which is directly irrigated by the coronary system.

Conclusion

Pharmacokinetics is a branch of pharmacology that studies the *temporal changes in the concentration of the pharmacon* in different compartments of the body.

Because the power of the effect has a parallel dynamic with the one of the concentration, knowing the concentration of a pharmacon at the action site is particularly important.

- Thank you for your attention!