C.1.11-1.12

Factors

that influence the effect of drugs

Changes

produced in the body under the influence of drugs

The dose theory

Dose

- the amount of drug used in one administration.
- one of the decisive factors on the drug effect.
- depending on the administered amount, drugs may have different actions.

By dose: we understand the quantity of drug which produces a certain pharmacodynamic effect.

From the intensity of effects point of view, three main types of dose are distinguished:

- **Effective dose (ED) (sin. therapeutic dose)**

  which produces a useful, efficient pharmacodynamic effect;
- **Toxic dose (TD)**

  that determines the appearance of toxic phenomena;
- **Lethal dose (LD)**

  which produces the animal's death.

We also know about the *threshold dose* (sin. subliminal dose)

the amount of drug that does not produce visible effects (or possibly at cellular level).

- Therapeutic range

The therapeutic index of a drug is a security measure of the drug.

The term of: safe area, that a drug ensures in its use, actually means the therapeutic range.

Quantitative measures for the therapeutic range, are represented by the ratio of different points on the lethality and dose-effect curve.

The therapeutic index is defined as:

$$T.I. = \frac{LD50\ (median\ lethal\ dose)}{ED50\ (median\ effective\ dose)};$$

- The higher is the value of this ratio, respectively the more distant are the curves from each other, the higher will be the therapeutic range.
- This measure has a drawback because it renders only the existing relations *when the curves are parallel*.
- If the curves are not exactly in the same inclination, the I.T. index defined above is not an accurate measure of the therapeutic range.

Factors

establishing a dose

A satisfactory answer can be expected only:

- if the drug reaches the place where it will act,
- at an adequate concentration.

The size of the animal

Within a species, size is a practical guideline to reach a specific drug concentration in the tissue.

In any case, *the animal's body-fat percentage must be estimated too.*

Dose variation depending on the route of administration
(after W. Cooke, 1994)

Route of administration	Etalon	Increased dose(%)	Decreased dose(%)
Oral (p.o.)	1	-	-
Rectal (p.r.)	-	150-200	-
Subcutaneous (s.c.)	-	-	75-50
Intramuscular (i.m.)	-	-	75-50
Intravenous (i.v.)	-	-	50
Intraperitoneal (i.p.)	-	-	50
Intratracheal (i.t.)	-	-	50

In this context, the individuality of an animal:

► can influence the effect of a treatment.

Examples:

- The use of strychnine, in nervous individuals can induce poisoning,
- Apomorphine may induce vomiting, only in some breeds of pigs (Landrace, Duroc).

Genetic factors

Some breeds may be sensitive to the action of drugs.

This can be explained by the absence of some specific enzymes (ex: *deficiency in glucose-6-phosphate dehydrogenase* in some breeds is associated with toxicity).

Such anomalies have led to the emergence of a new branch, *pharmacogenetics*.

When response to a drug is qualitatively or quantitatively abnormal , *idiosyncrasy* intervenes.

Sometimes idiosyncrasy can be explained genetically.

Susceptibility

is the term used to describe an abnormal quantitative response and is demonstrated by the so-called *hyperactive* (a patient particularly sensitive to the action of a drug).

Such variations frequently dependent on the *atypical elimination rates*.

Species

Among the species of animals, there are some examples of extreme resistance or sensitivity to drugs.

Species influence the effect, the cause being mainly : genetic or morph pathological factors.

There are species that react differently to the same drug.

Examples :

- Dogs react to morphine through hypnosis or vomiting, whilst
- Cats and large ruminants will react to the same drug through over excitement / hyperactivity

- in cows alcohol is well supported as a narcotic, whilst horses are sensitive,
- chloralhydrate, is very effective in horses, but it is hardly supported by cows.
- Apomorphine in dogs, produces vomiting constantly, whilst in pigs its action is inconsistent.
- Vomitive drugs in omnivores and carnivores can become rumenatorics in ruminants.

- Sensitivity depending on the species :
  - Pigs and poultry to salt,
  - large ruminants to mercury
  - cats to phenolic drugs.
- Doses in ruminants, increased by 20-40% compared to equines, (drugs stagnate and even suffer decomposition in the forestomach.

In the case of improved breeds, the effect of the drug may be altered *due to sensitizing genetic factors*

Examples:

- Arabian thoroughbred horses,
- Supercuni rabbits,
- Cockers etc.

Equines and some dog breeds are sensitive to injectable Ivomec, due to the permeability of the meningeal blood brain barrier common in some individuals.

In case of using drugs that are common for human and veterinary use, the doses for animals are:

Species	Increasing the dose from humans
Cow	x 24
Horse	x 16
Sheep	x 3
Goat	x 3
Pig	x 3
Dog	Equal to that of humans
Cat	½ of the human dose

Correspondence animal-human dose
(after Suciu, 1990)

Examples:

If you would take a standard adult man (aprox. 70 kg) then the required dose is equivalent with a dose for a 10 kg dog.

Even if small ruminants (approx. 40 kg) are four times heavier than the dog above, they will only need a dose twice as high.

- a pig (approx. 100 kg) will receive a dose, not ten times higher but only four times higher compared to a 10 kg dog.
- a horse (approx. 400 kg) will require doses, only ten times higher than the dog from the example, and
- large ruminants (100-400 kg) will be treated with doses of 10-15 times higher.

So,
the smaller sizes they have, the higher doses reported per kg body weight they can handle.

For example,

a 2 kg cat will not receive, 20% from the dog's (10 kg) dose, but much more, like 50%! The same is true for birds (2 kg) who will receive 40-50% from the dogs‘ dose.

Anatomy of the digestive system

In ruminants, food passage rate is slow, and the intestinal content is large, in comparison to the rate of absorption.
Therefore, there is much time available for absorption, while the large volume of intestinal content dilutes the orally administered drug, thus slowing the rate of absorption.

- One problem is related to the compartment into which the orally administered drug enters, influenced by the work of the esophageal tray.
- Drugs with weakly alkaline character tend to accumulate in the weak acid ruminal juice, which has a very large volume in ruminant species.

Age

Very young and very old animals generally require the administration of reduced doses due to the possibility of organ dysfunctions .

In old animals dysfunctions are mostly *degenerative*, at the hepatic and renal level.

In young animals excretory and metabolic functions *are not yet developed* (ex: chloramphenicol, is toxic for piglets due to the absence of a suitable enzymatic equipment).

- youngsters, infants, will receive reduced doses with 30-40% (small animals) or even 50-70% (youngsters up to 1 year old in large animals).
- There are situations when, compared to adults, youngsters are more resistant to therapeutic doses (ex: barbiturates in piglets).
- they will receive doses reduced by 20-40% because the activity of some enzymatic systems may be reduced or even abolished.

Doses by age categories (after Balaci)

Species	Category	Expected dose
Equines	3 - 15 years	1 dose
	15 - 20 years	¾ dose
	20 - 25 years	½ dose
	Foals 2 years	½ dose
	Foals 1 year	1/12 dose
	Foals2-6 months	1/24 dose
Cattle	3-8 years	1 dose
	10-15 years	¾ dose
	15-20 years	½ dose
	Calves 4 - 8 months	1/8 dose
	Calves1-4 months	1/16 dose
Sheeps and goats	Over 2 years	1 dose
	1-2 years	½ dose
	Lambs and kids 6-12 months	¼ dose
Swines	Over 1,5 years	1 dose
	8 - 18	½ dose
	Youngsters 4-9 months	¼ dose

Gender

Gestation involves contraindications (ex: purgatives or corticosteroids, which can induce abortion).

Teratogenic effects are investigated and taken into account in the evaluation of each new drug (for veterinary use too).

The elimination of drugs by milk is another example for toxicity risk related to animal gender.

Time

of administration and pathology

A drug administered orally, is more rapidly and completely absorbed if the anterior digestive segment is empty, but often, can be irritating to the tissues.

The recognition of the existence of the circadian rhythm within physiological functions has already found application in drug administration.

- Generally, sick animals have a diminished drug detoxification capacity.
- An increased or decreased rate of intestinal passage will change:
  - absorption period, and therefore,
  - the proportion of the absorbed dose.

- Hypoalbuminemia decreases the coupling rate.
- Heart failure will be accompanied by liver and kidney failure.
- Enteritis reduces intestinal transit time and therefore may reduce the absorption of drugs.
- Peripheral circulation is inadequate in states of shock of any origin, preventing absorption of s.c. injections.

- Tolerance and intolerance

- *tolerance* to a drug disappears with the discontinuation of the treatment (ex: dogs may exhibit tolerance to the narcotic effect of barbiturates).
- *resistance* to drugs can occur for many reasons ex.:
  - when a drug is a specific antigen, and antibodies may be produced for it, inactivating it;
- For example: the metabolic resistance of Trichostrongylus population to therapeutic doses of benzimidazoles.

- Therapeutic indications

This assessment is purely therapeutic and includes :

Dosage adjustment based on the nature of the disease and depending on the causative agent (ex: therapy of acute fascioliasis require higher doses of the same drug as in the chronic form).

- Often the use of high doses is similar to increasing the risk of toxicity, to the benefit of receiving increased effects.
- Certain antibiotics are so toxic that their systemic administration is done only in case of emergency (ex: polymyxin).

Concomitant

drug therapy

Concomitant use of several remedies requires the introduction of several variables in calculating doses, because of the potential interactions between the administered components and patient.

Use of *"shot-gun"* type products or *polypharmacy* (active substances associated without a certain diagnosis) is a simple substitute to a certain, professional diagnosis, often with *undesirable implications*.

- Amplified response

To reduce the incidence of toxicity, one or more drugs can be administered simultaneously.

- The final answer can be quantitative = with the amount of expected responses in the case of independent administration = *medication summation*
- If the answer is higher than what can be explained by simple summation, we are dealing with the effect of potentiation *or synergism*.

- Diminished response

- In multi-drug therapy it happens for the observed response to be smaller than the sum of the components' responses = *antagonism* between the drugs used.
- sometimes the antagonism can be explained by the fact that a drug interferes or performs an action, opposite to the other.
- the antagonism is often dependent on a mechanism that involve pharmacological / physiological incompatibility.

- Incompatibilities

- The associated components may be incompatible:
  - physically or
  - chemically, when reacting with each other

- Often, the need for administration, tempts the clinician to combine remedies.
- In the case that, the compatibility of the remedies is unknown, concomitant use is contraindicated.

- Amplified toxicity

- The toxicity of a drug can increase several times, depending on the situation.
- Two drugs whose degradation pathways *are the same*, can enter in competition if, the metabolic pathway has limited capacity.
- If one of them has a narrow therapeutic range, toxicity is facilitated.
- *Competition for coupling sites is another mechanism* which may increase the risk of toxicity of drugs that engage massively to proteins.

- Drugs whose plasma half-life is much shorter than the biological half-life, the so-called: "*hit-and-run*" (achieve plasma levels rapidly, but are eliminated as quickly) cause increased responses to other drugs.
- *Pharmacodynamic incompatibility* is the use of adrenaline as a cardiac stimulant in an animal anesthetized with a drug that sensitizes the heart to adrenaline action (ex: cyclopropane).

- Reduced toxicity

- A common example of low toxicity can be the pre-medication with tranquilizers before the induction of anesthesia.
- This simplifies the process of induction and reduces the dose of barbiturate required, therefore, it is useful in reducing the risk of anesthesia.
- The antidote use in poisoning exploits both pharmacokinetic and pharmacodynamic interactions (competitive antagonism) in the benefit of the patient.

Factors

that determine the frequency of administration

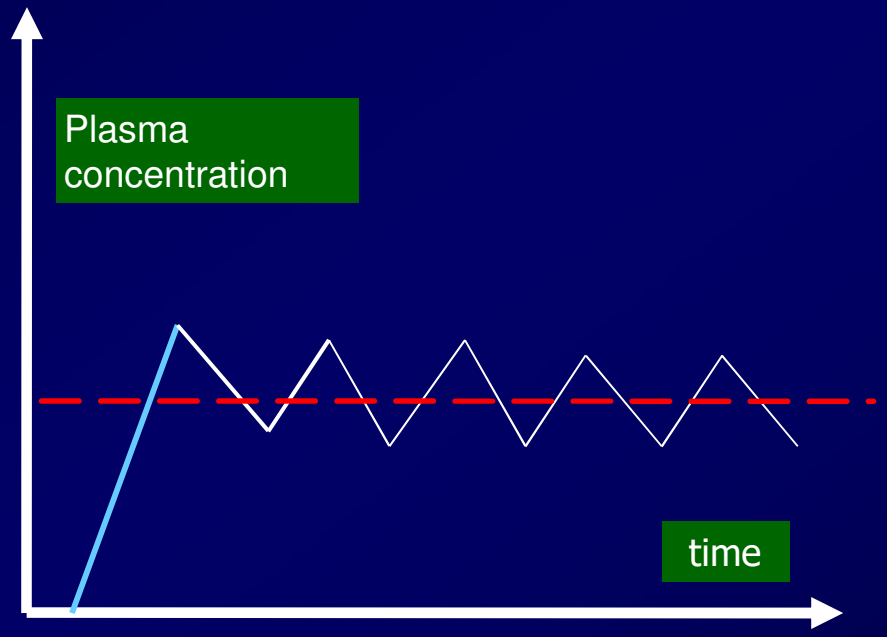
- In the treatment of diseases, the initial goal is to achieve an adequate response.
- This fact depends on the suitable concentration of a drug in the bio phase.
- An appropriate therapeutic effect often asks the drug to act over a longer period of time.

Clearance of drugs

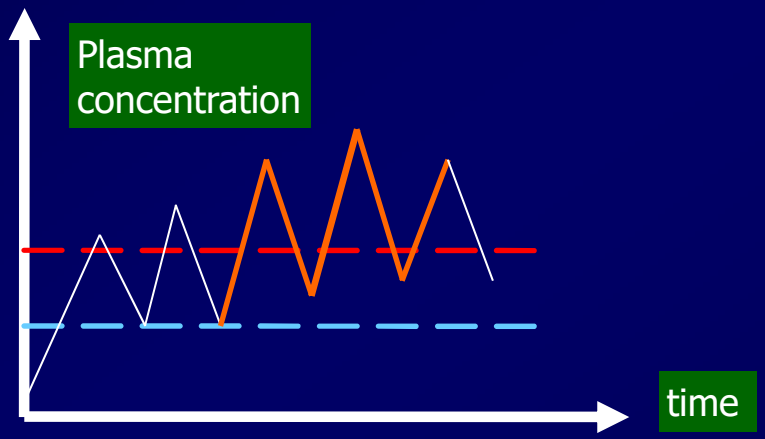
The shorter the half-life is, the quicker the product will be removed from the body and the shorter the interval between administrations will be (when necessary to maintain a constant level of effect).

- Because, the belief that there is one standard interval between administrations is incorrect, the size of repeatedly administered doses will vary according to the benefits.

For example, an initial attack dose, followed by a daily maintenance dose is a procedure often used with sulphonamide therapy



The probable plasma level originally obtained by administering an attack dose, which reaches desired plasma concentration, and then, by administration of lower maintenance doses;



When the level obtaind by administering a dose, does not return to the initial value before the next dose, concentration may increase successively with each dose, this phenomenon can produce a cumulative toxicity.

- *Coupling to plasma proteins* will suppress:
  - inactivation and excretion rates,
- extensity or the power of coupling can vary considerably for the same drug in several species or within a family of drugs, when it is tested on different individuals.

- Cumulative toxicity is characteristic for compounds with half-lives exceeding the interval between administrations and when dose size allows the cumulation phenomenon to progress beyond the therapeutic level, (thus falling within the toxic concentration).

- Concentration stability

- Besides the mentioned factors, the frequency of administration can exert considerable influence, not only on the duration of action of drugs but also on the quality of drug action.
- Generally, a greater concentration stability is achieved when a *pro die dose* is administered on several occasions over a period of 24h.

Establishing

rates of drug dosing

The rate of: absorption, distribution and elimination can be experimentally quantified through *the apparent volume of distribution,* where the level of a drug in the body, can be estimated at any time when plasma concentration is known.

- Using these pharmacokinetic parameters and on the basis of the calculations it is possible to issue rational recommendations about the size and frequency of the dose.

Establishment of dose size

- If a drug acts quickly, achieving immediately observable effects in an animal, dose determination is possible only through the continued use of the drug until the desired level of response is reached.
- Dose titration according to the response is easy, for instance, when administering i.v. use anesthetics.
- The only requirement is to know the exact intensity of the desired effect, before starting the administration.

- In the case of a drug whose effect is manifested slowly or can not be measured clinically, the approach will be different.
- For some groups, the concentrations may be set based on *"in vitro"* studies (ex: identification of concentration at which antimicrobial agents inhibit the growth of bacterial cultures).

- This, multiplied by an appropriate safety factor (generally = 5) = necessary concentration in the body fluids
- For the other groups of drugs, the study is based on the measurement of plasma concentrations, when it is assumed that the response has reached the desired level.
- In each case, the dose calculation which implies reaching such concentrations is made using this relation :

$$D = Cpd \times Vd$$

where:

D = dose (mg),

Cpd = desired plasma concentration (mg l-1),

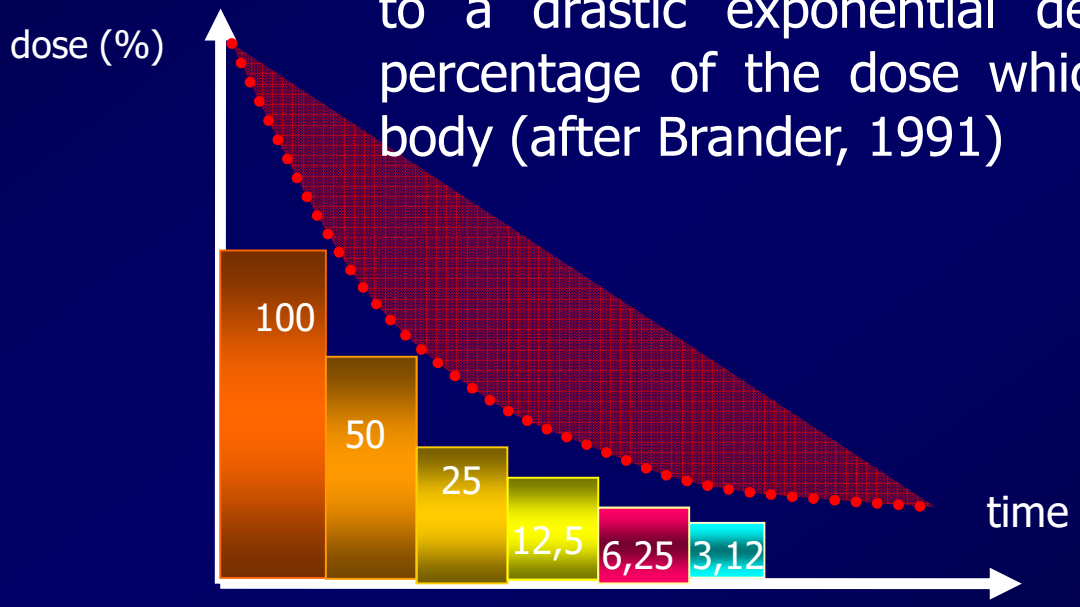
Vd = apparent volume of distribution (l.).

- when the drug is not administered i.v., it may be necessary to apply a correction factor that takes into account the incomplete bioavailability of the dose.

Establishing the frequency of administration

- The single dose has a duration of action determined by:
  - the size of the dose,
  - the elimination rate constant and by
  - the apparent volume of distribution.
- If the minimum plasma concentration required to gain a therapeutic effect is known, it will be possible to calculate: the time required to decrease the initial concentration to this level.

The elimination of half of the drugs' amount in the body by the end of a half-life, will lead to a drastic exponential decrease, of the percentage of the dose which exists in the body (after Brander, 1991)



Establishing intravenous infusion rate

- When a therapeutic effect of constant intensity is necessary, this requirement can be satisfied by iv infusion at a suitable dosage rate.
- The rate at which the drug is lost from the body may be most useful, expressed as total clearance, when the desired plasma concentration is known or can be found out (Cpd):

$$R = Cpd \times Vd \times ß$$

Where:

R = loss rate of the drug (mg h-1).

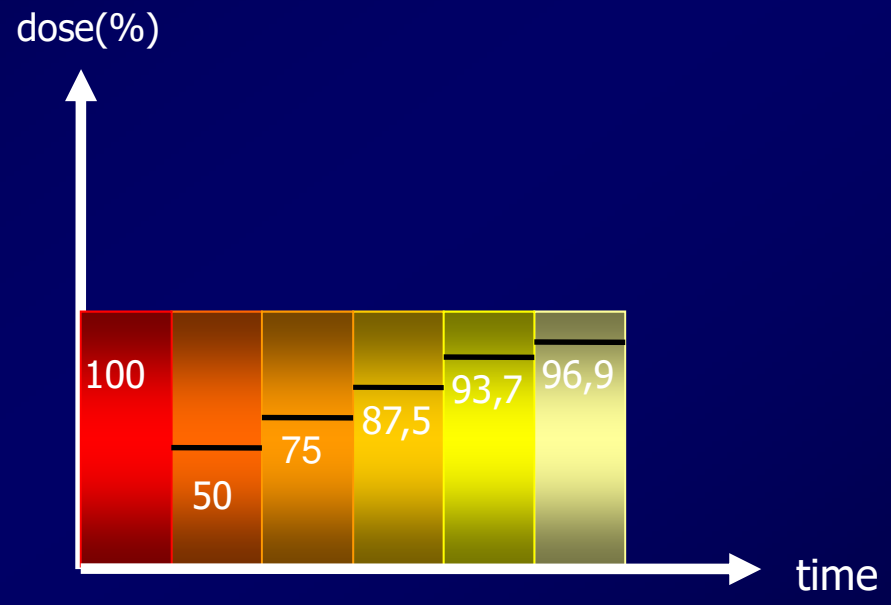
So,

to maintain a constant level of an already achieved drug concentration, it is only necessary to perfuse the drug *with an hourly rate equal to the rate of elimination*.

Plateau effect

- Achieving a stable plateau concentration is possible without the administration of an attack dose.
- The disadvantage is that, the time required for the therapy may be incompatible with the desideratum of a favorable therapeutic outcome.
- The amount of drug excreted per time unit increases progressively as long as a continuous infusion of the drug will cause progressive increase in plasma concentration.

- The time to reach plateau concentration and that required for complete removal, is approximately equal to = 6 x t½ .
- The progressive achieving of a plateau concentration is illustrated in the figure, where: the total amount of the drug in the body represented on each half-life period is equal to the amount infused over the duration of the half-life plus the residue of infusion until then.



The accumulation of a drug in the body when it is injected at a constant rate of 100 units / Half Life(after Brander, 1991)

The effect of

repeated administrations

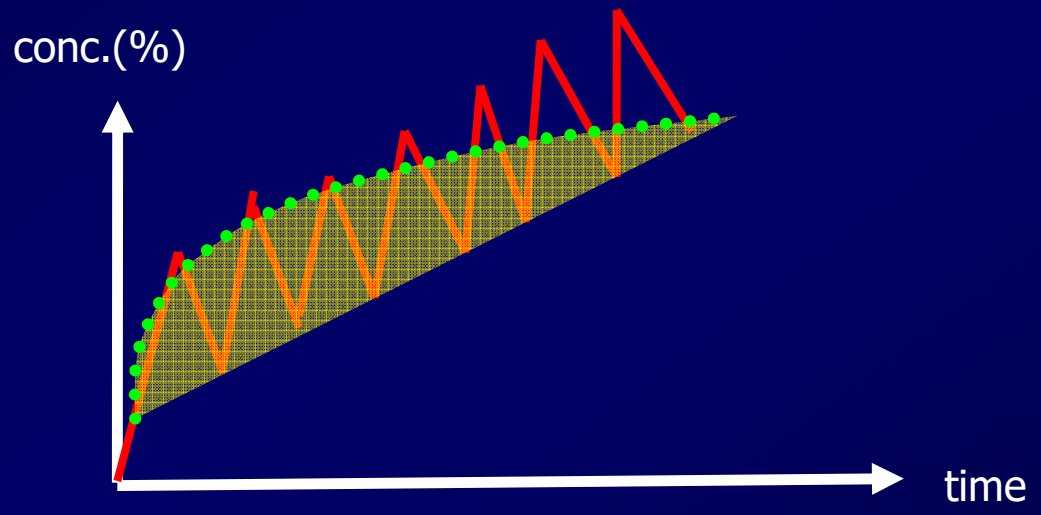
- The possibility of reaching an approximate plateau effect by repeated administrations is known, and if:
- the size of the dose and the dosing interval are held constant, the required average plasma concentration can be achieved and maintained for a desired period.
- So, the amount of drug in the body and the plasma concentration will be at a maximum, immediately after each administration and at a minimum immediately before the next dose.

- Starting from the idea that the minimum concentration is not incompatible with the therapeutic purpose and the peak concentration does not imply toxicological risk, plasma concentration oscillations are acceptable.
- Oscillations can be reduced by dividing the daily maintenance dose in lower equal doses, administered at shorter fixed intervals,meaning, an approach by the principle of infusion.

The plasma concentration in the range of stability **will be provided by formula:**

$$Cp\infty = \frac{1{,}44\ fD}{Vd}$$

Where: $Cp\infty$ = The mean plasma concentration plateau, and
fD = bioavailable dose.



Fluctuations in the plasma concentration of a drug that is administered at intervals of a constant rate equal to the half-life. To note that after about four doses, a relatively constant average concentration is obtained. (after Brander, 1991)

- Administration at longer intervals than the half life virtually eliminates the possibility of cumulation.
- At an interval shorter than the half life, the index increases rapidly, cumulation occurs in a higher degree, and the concentration plateau has a higher level, as long as the size of the dose is not reduced.

The practical consequence of these features :

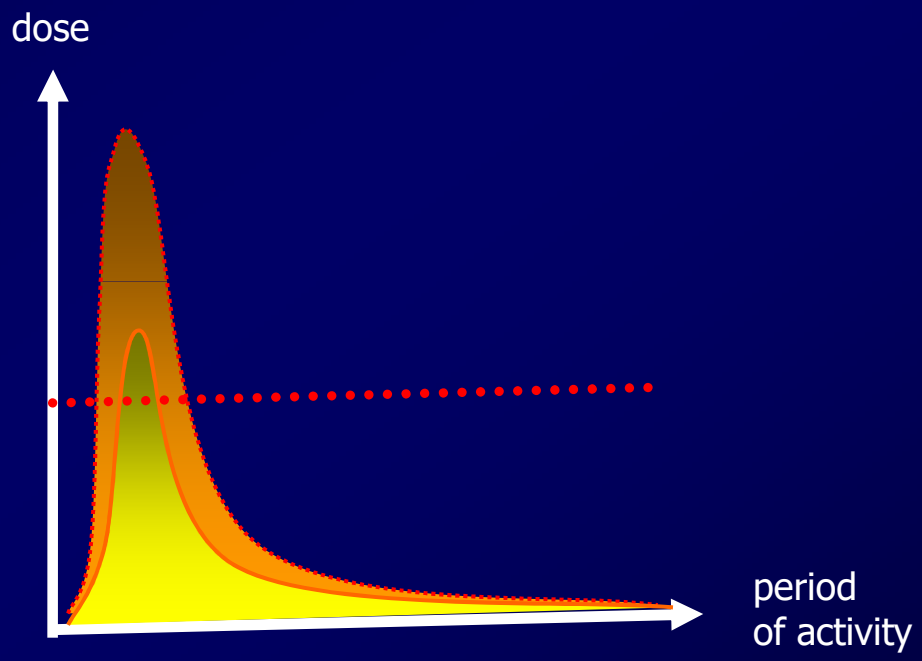
Drugs that have a *short half-life* (4h) can be administered in maintenance doses based on conventional fixed interval (ex: once every 8 hours) so that the therapy will not lead to cumulation or reach a plateau concentration sufficiently high to result in toxic effects;

The tendency of drugs to accumulate is expressed by a value named : cumulation ratio

It is defined by the ratio:

$$\frac{\textit{the amount of drug in the body after the first administration}}{\textit{amount during the peak of the plateau (plasma peak)}}$$

When first order kinetics are operating, a doubling of the duration of effect is obtained by increasing the administered dose by four times (Brander, 1991)



- drugs with a longer half-life (ex: phenobarbital, oxytetracycline etc.), when administered at a maintenance dose and at the same frequency (less than the half life) *will accumulate to dangerous levels* or will require a long time to reach an acceptable plateau level when they are administered at intervals equal to the half-life.

This problem is solved by abandoning the fixed dose and raising the *initial dose*, which rapidly rises up to the therapeutic plasma concentration level, that will be followed by *conventional doses (maintenance)* which will maintain the desired concentration.

Sulfonamides and antibiotics are groups for whom a rapid onset of action is needed, but have a long half-life and narrow safety margins and therefore, are managed by the scheme: *loading dose + maintenance doses*.

If you know the maintenance dose, the loading *dose can be calculated by the following relation*:

$$Dl = \frac{Dm}{ß \times t.int.}$$

Where:

- Dl = loading dose,
- Dm = maintenance dose,
- ß = elimination rate constant,
- t.int. = interval between doses.

Stereospecificity

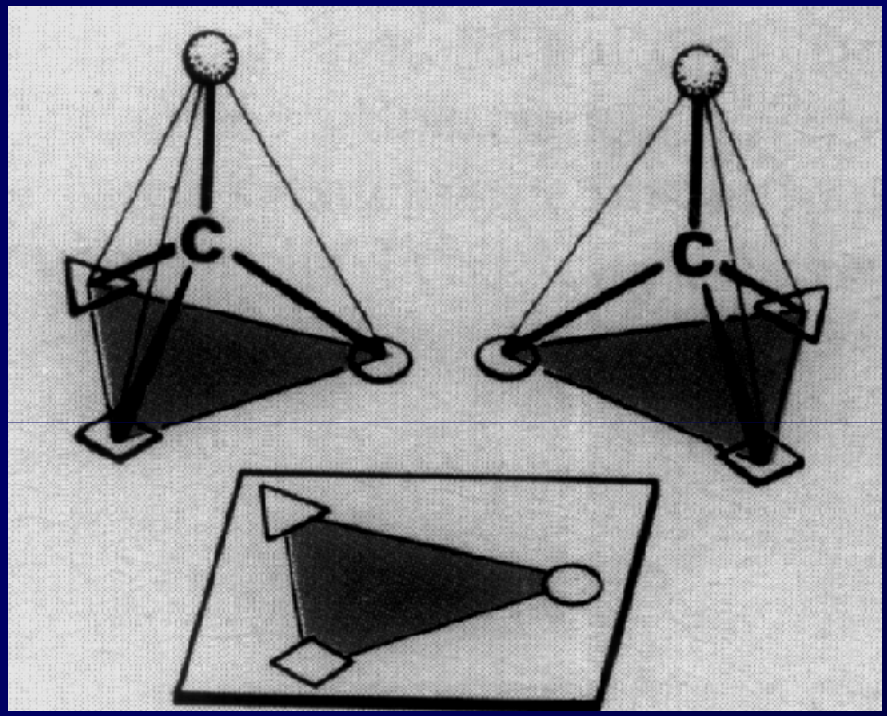
of drug action

- The alleged action of a particular drug is based on the preferential binding of a substance to a specific molecular reaction partner, namely to a receptor.

  The special affinity of a pharmacon to its “own” receptor implies that it has a configuration that fits very well and that there is some degree of complementation between the two partners.

- A form of stereoisomerism is enantiomer.
- Is the isomerism in which the spatial structures of two substances (enantiomers) are symmetrical to a plane = *“mirror image”*, and their images are not *"congruent"*.
- Enantiomery is based on the fact that in a molecule there is a carbon atom bearing four different substituents.

Stereoselectivity receptor occupancy. *Only one of the two enantiomers (left) has features complementary to the site of receptor coupling*. (after Kuschinsky)



- Distances between a given atom and neighboring atoms are identical in enantiomers.
- Enantiomers are comparable to one another in almost all chemical and physical properties.
- They differ however, in their optical activity, because they rotate the polarized plans of a beam of polarized light in different directions.

The beam of polarized light will be rotated :

- to the right *by the (+, dextrorotatory) form* and
- to the *left by the (-, levorotatory) form*.

Independent from the direction of rotation of polarized light, the characterization of both enantiomers is possible by means of two classification systems.

The classification is done by dividing the substances in:

- D-*(dextrorotatory)* and
- L-*(levorotatory)* glycerine aldehyde,

thus obtaining Series D and Series L.

- Taking into account the location of substituents on the asymmetric carbon atom and their number, it is possible to classify them using the R-S system.
- In the chemical synthesis of a substance with an asymmetric carbon atom, often the result is a mixture (racemase), in which the enantiomers have the ratio of 1:1 and they do not produce the rotation of plane polarized light.

In nature, the controlled enzymatic synthesis takes place *stereo selectively*, such that only one of the enantiomers is synthesized:

(-),D,R-adrenalin, (-),L,S- hyoscyamine.

When the asymmetric center of a molecule`s pharmacon is found in the area of its coupling with the receptor, and three of the groups linked to the asymmetric carbon participate in the binding, then only one of the enantiomers will present optimal complementarity with the receptor.

Different spatial structure,

Can influence the complementarity of enzymes involved in the metabolism of the drug, so that the metabolic transformation of the enantiomers will be carried by different routes, stereo selectively.

Example:

The (more active) (-), S enantiomer of warfarin (oral anticoagulant) will be decomposed in the liver, at the level of the coumarin cycle,

During this time the (+), R enantiomer will be changed especially at the level of the carbon atoms chain.

Therefore, the elimination of the S form occurs faster.

Zero-order

kinetics

- Describing the kinetics of absorption and elimination and their consequences on the size of the dose and their frequency, it started from the idea that these processes apply first order kinetics.
- One of its characteristics is that the half life for the influenced process (usually elimination) is dose-dependent.

- When zero-order kinetics is applied, a *constant amount is circulated, rather* than a constant fraction *per time unit*.
- It is also assumed that when the rate constant for a given drug in a particular individual stabilizes, it will remain unchanged.

- Such a change during treatment would inevitably produce a significant deviation of the initial plasma concentration, with unwanted consequences (ex. inadequate absorption, excessive drug action or toxicity).
- It is possible for a drug whose elimination is dependent on the carrier transport processes, to be maneuvered through first order kinetics until the carrier is saturated. In that moment the kinetics become order zero.

Drug

residues

The existence of drug residues in milk or edible tissues of animals is a concern of public health interest.

To reduce the risk involved by residues in food of animal origin, the legislation requires for *a period called the waiting period, period of prohibition or withdrawal*.

- Initially, problems caused by the persistence of O.C. in the body fat stores and the undesirable effects on the farm animals, initiated the domain.
- O.C. has a high partition coefficient, thus large amounts are entering the body fat where they remain stable and can be released in time.
- The persistence of chemical substances and the realization that the milk that contains antibiotics (ex: betalactams) induces sensitization phenomena in humans, have focused the attention on the toxic potential of residues.

Pesticide residues in dairy products, antibiotics, growth promoters, hormones in meat are detected frequently.

These and the safety concern for consumers that are regularly exposed to chemicals led to define a unit called: ADI = acceptable daily intake

The value of this quantity for a human, represents the daily intake of a substance through food, which, per unlimited period, can not produce undesirable effects.

This depends on the *known toxicity* of the substance and is calculated by the relationship :

$$ADI = \frac{NEL \times 70}{100}$$

Where:

NEL = ineffective quantity (mg kg-1)

NEL = "*no-effect level*" deducted from p.o. administration of substance to rodents, per long-term

Factor 70 = derived from average body weight of a human (adult human is considered to be 70 kg)

100 = arbitrary factor of safety (can increase up to 2000 in the case of carcinogens)

- Residues may occur, not only because of the physicochemical properties of the substances themselves but also because of the effectiveness of pharmaceutical and bio-engineering devices that try to increase the half-life of the drug in question (bowls whit sequential or continuous removal, implants etc).

The risk - benefit ratio

- Before starting a treatment, the physician should choose the drug that will produce favorable changes in the health status.
- Also, he must be sure that he knows how to properly use the drug to obtain not only the *type* but also the *level of response* he wants to get.

- He must know the *disadvantages* that might be involved in the therapy with the product in question or the *discontinuation* of treatment.
- If the doctor has information, he can decide if the benefits of using a drug, outweight the disadvantages of administering or withholding the drug.
- This is *the risk – benefit ratio*.

If the veterinarian decides *in favor of therapy*, he can also make a decision regarding the *cost-benefit ratio*, in case of farm animals.

Obviously, this decision involves an adequate knowledge of the available information and the ability to consider these and other factors.

The term: *hazard* is used to describe the nature of any possible disadvantage produced by drug use (ex: hypersensitivity to penicillin)

The term: *risk* is used to describe the likelihood of the hazard to occur in that case

Examples:

- Occasionally, phenylbutazone in horses causes death
- Diethylstilbestrol (DES) hormone, used as a growth promoter, has been reported to induce cancer in humans and animals (as same as clenbuterol).
- Anticancer substances *can cause cancer* and, in any case have numerous side effects.
- Oxytetracycline produced fatal colitis in horses.

Estimation of

the risk-benefit situation requires numerous data and, in European countries, the recording of all adverse effects that may occur in animals, or Veterinary pharmacovigilance, began in 2000.

- Veterinary pharmacovigilance

- Alerts about adverse reactions to drugs as a result of the treatment in animals urged the doctors to classify the main causes of these shortcomings.
- Trying a definition, *veterinary pharmacovigilance* is an operation of registration, monitoring and systematic evaluation of side effects that occur as a result of inappropriate medication with some veterinary drugs.

Reasons of unwanted reactions are:

- Poor (clinical phase) experimentation of drugs advertised "aggressively" by firms producing drugs.
- excessive prescribing of only a few groups of drugs (polypragmasia) to the same herd (ex. sulfonamides, chemotherapeutic agents, antibiotics, antiparasitic).
- increased “aggressiveness” of the new syntheses;
- The biological peculiarities of each case;
- The interactions between drugs from the associations.

Veterinary Pharmacovigilance has two objectives:

1). The quickest possible detection of unexpected reactions (in animals);

2). determining the frequency and incidence of the already known or recently found adverse reactions, that are produced by veterinary drugs.

Dose-effect

relationship

- The investigation of dose - dependent *response variation* was one of the starting points of pharmacotherapeutics.

  This fundamental relationship has made the development of *quantitative bio determination* possible and stimulated the proposals for the description of the quantitative consequences of couplings between drug and receptor.

Two types of responses are known:

- In the first case, the answer is an event whose frequency of occurrence in *a population* is *dose-dependent;*
- Secondly, the intensity of the response in *an individual* is dose-dependent.

The dependence of a drug effect, on the dosage or on its concentration, is a characteristic function for each substance.

In drug testing, a *positive result* is, conventionally, the occurrence of a response of a predetermined intensity, while an increased dose will determine that a higher percentage of the treated animals respond with the same intensity.

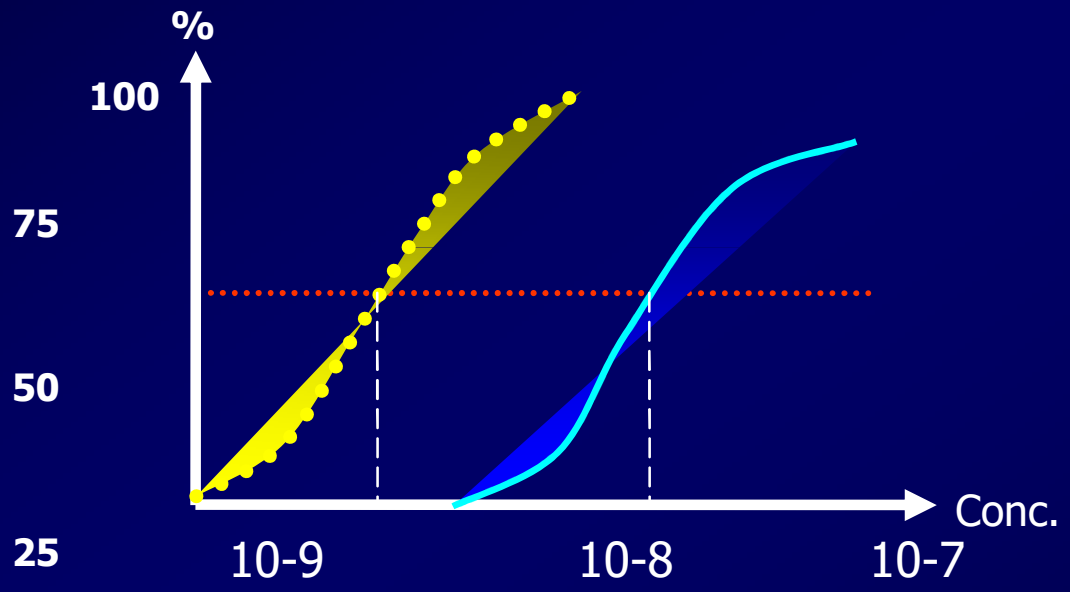
This function is represented graphically by a *dose - effect* curve from which the following three values can be extracted:

- *affinity,*
- *maximum possible effect ("intrinsic activity") and*
- *the ascendant curve.*

it will be noted on the abscissa: *the dose* or *the concentration,* in logarithmic expression,

- on the ordinate: *the reaction expressed* as a percentage from the maximal possible effect.

Concentration-effect curve for acetylcholine (dotted curve) and for arecoline (solid curve) in an experiment carried out on guinea-pig ileum. On the abscissa: the molar concentration expressed logarithmically; on the ordinate: effect represented as a percentage from the maximal possible effect. (after Kuschinsky)

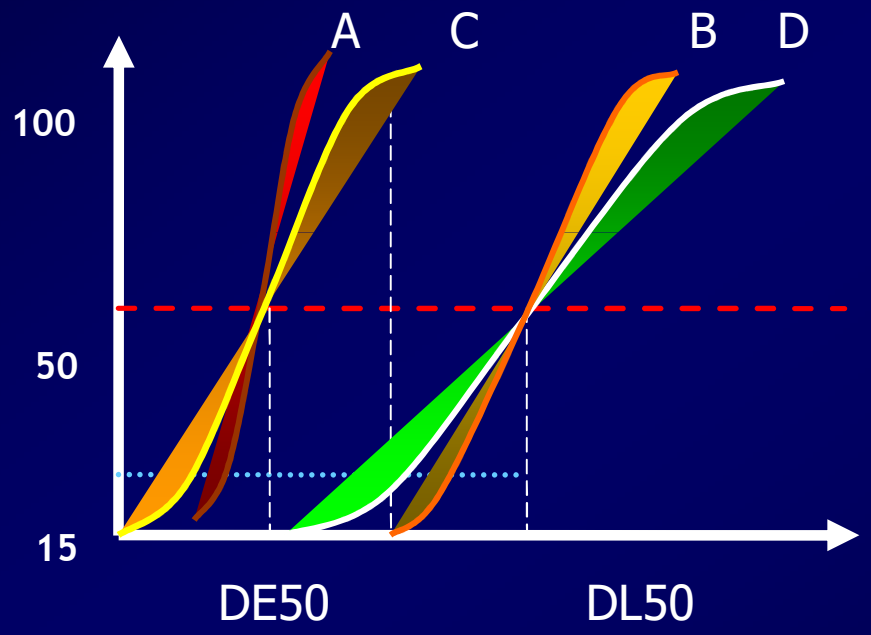


The potency of a drug:

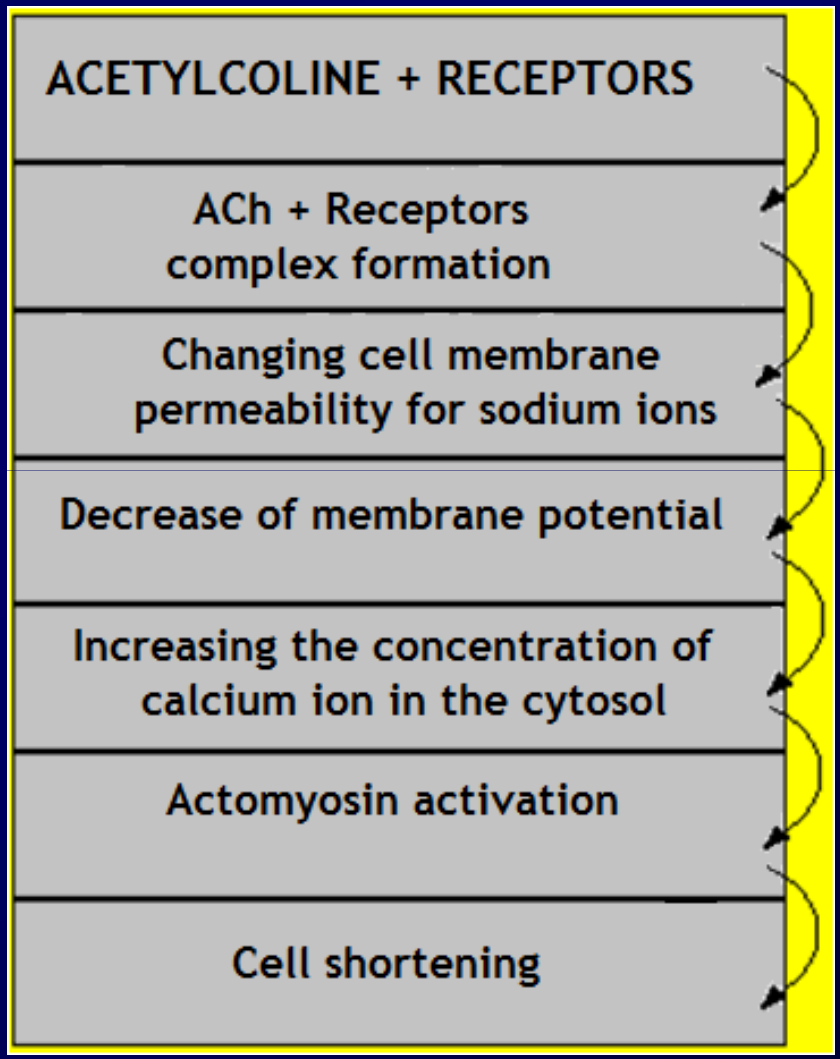
- A property determined by the pharmacokinetic behavior, the ability to occupy and then activate receptors, represented by the distance between the vertical axis and the leg of the curve.

Potency has a practical importance only when it is considered as a relation between the *dose-effect curve* and *dose-lethality curve* (where the animal's death is recorded as a result) for the same drug.

Dose-effect curves (A si C) and lethal dose (B si D) of two anesthetics which have the same DE50 and the same DL50, but whose curves have different inclinations. These drugs must have the same therapeutic index, but the superiority drug A is obvious, which has a better therapeutic report. (after Brander,1991)



The transformation of receptor occupancy in effect. Interaction between acetylcholine and specific receptors translates as chain reactions leading to cell shortening (after Kuschinsky)



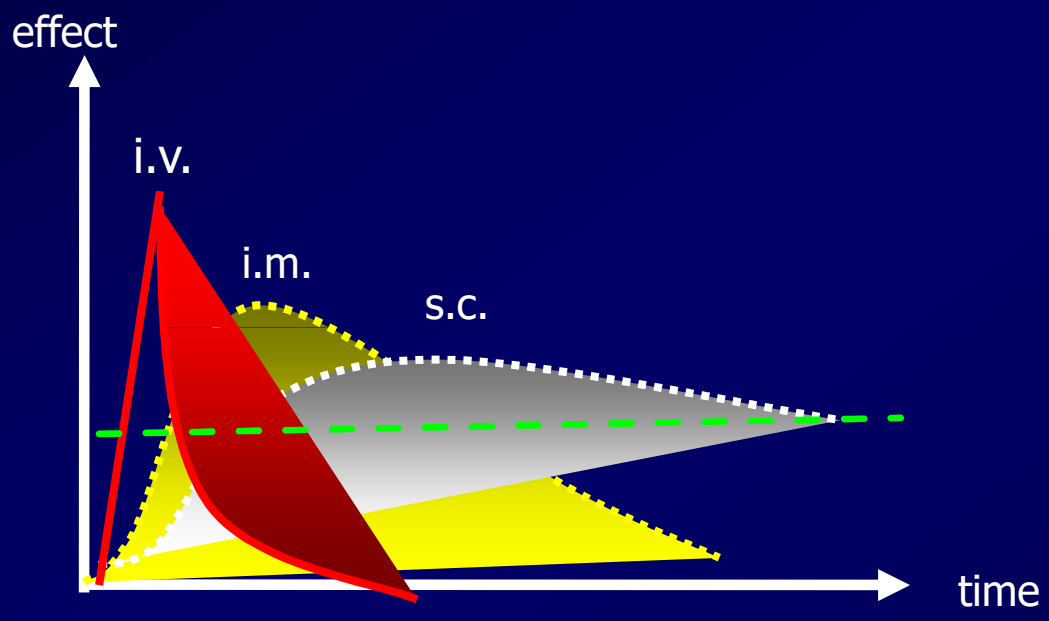
- Latency and intensity

Latency period

is the time elapsed from the end of administration and the moment when the concentration of a drug at the site of action is sufficiently large for the drug to be capable to exercise its characteristic effect.

The time taken to reach that concentration will depend on the following factors :

- *dose*, the concentration at the site of administration influences the size of the concentration gradient of the central compartment.
- *rate constant*, the fraction of the drug which is absorbed at the site of administration per time unit .
- *absorption by diffusion*, *which* follows first order kinetics, maximum absorption will appear shortly after administration. As the quantity at the site of administration drops, the absorbed amount will be reduced per time unit.



There is an interdependence between:

a) the route of administration of a standard dose of the drug,

b) the latency period,

c) maximum concentration that may be achieved and

d) duration of action.

The duration

of action of a pharmacon

- After a unique iv administration, the entire dose will be present in the central compartment and so, will be exposed to first order elimination process.
- As the concentration in such a process is higher, the proportion removed per time unit, is greater (concentration decreases exponentially and fast).
- Longer duration for other injectable routes and lower maximum concentrations reflect the full absorption period required.

- For both the s.c. as well as the i.m. path, the plasma *peak* coincides with the period the rate of introduction of the drug into the central compartment coincides with the elimination rate through processes of elimination.

Applying the elimination rate constant to the quantity of drug in the body, *the eliminated fraction per time unit* can be calculated.

The duration of drug effect

Depends on the time required to decrease the plasma concentrations below the minimum active value.

This in turn, is determined by the distribution volume of the drug (the greater the volume, the higher the time for elimination) and the relative contributions of the various mechanisms of the removal process.

The expression of inconstancy, in relation to metabolism and excretion can be observed in the variation of the plasma half-life, in a particular species and a particular drug.

Example:

Oxytetracycline has a 6h half-life (t1/2) in dogs and 10h in horses, while t1/2 of chloramphenicol is 6h in dogs and only 1h in horses

This highlights the lack of safety when extrapolating doses from one species to another based on body weight.

Influence on the duration of drug action, mechanism of distribution and excretion (after Brander, 1991)

Distribution volume	Excretion mechanism	Half-life
Plasma	Glomerular + *active tubular*	3 minutes
SEC	Glomerular + *active tubular*	15 minutes
	Glomerular + *active tubular*	50 minutes
Total water	Glomerular	4 - 5 hours
	Glomerular but with 99% resorption	25 days
SEC (High coupling affinity)	Glomerular + *active tubular*	50 days

The plasma concentration

is frequently measured as an *indicator of the useful length of life of a drug in the body* and one must not forget, that the forces that strive to alter this level, operate continuously.

These forces can be divided into:

- those which tend to increase concentration (absorption, biotransformations for activation and release of the coupled drug) respectively,
- those that tend to decrease concentration (biotransformations for inactivation, storage in tissues and excretion of drugs.

First-pass

effect

- This effect contributes almost in all cases, to the appearance of differences in the bioavailability of an administered drug.
- Intestinal absorption (except the sublingual or rectal ones), before reaching the systemic circulation, leads the drug through the portal circulation.
- Therefore, it will be exposed to extraction from circulation and inactivation.
- For some drugs (ex: griseofulvin) even a single hepatic pass, can lead to extensive loss of substance.

Gastric acidity

- destroys penicillin G,
- proteolytic enzymes attack polypeptide drugs (insulin).
- tetracyclines form chelates with the calcium in milk, and
- penicillinase secreted by E. coli, reduces the availability of a quantity of penicillin (ex: benzylpenicillin)

Intestinal mucosa

may inactivate some orally administered drugs in a substantial degree through :

- hydrolysis (ex: glycerol trinitrate),
- decarboxylation (ex: levodopamine), or
- sulphates formation (ex: isoprenaline).

- Thank you for your attention!