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Body's response to medication

Practical

elements of veterinary therapeutics

Sursa imagine: http://www.petconnection.com/blog/wp-content/uploads/2010/09/veterinarian.jpg

See: www.veterinarypharmacon.com

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1.

In the study of drugs in vitro tests are made.
The most important is:

The dissolution rate, because it determines the rate of absorption.
These are corroborated with in vivo testings.
Based on following a drug concentration in blood or urine it can be determined the:

- dissolution constant;
- absorption constant;
- biological half-life;
- elimination constant;
- other parameters (using equations or graphical methods).

Generally, *biological availability* increases *in direct proportion* to *the rate of dissolution.*

each type of pharmaceutical formulation has its own behaviour (ex. Oral formulations increase their biological availability from dragees → aqueous solutions).

In hygroscopicity testing, are taken into consideration: the *bioequivalence* and *the clinical results of the treatment*.

In terms of the doses used, it can be:

Median effective dose ED_{50}

represents the dose inducing **positive effect for 50%** of the individuals of a population.

Ideal dose ID_{99}

represents the dose inducing a **positive effect for 99%** of the individuals of a population.

Lethal dose LD_{50}

represents the dose inducing **lethal effect for 50%** of the individuals of a population.

Unjustified increase of doses causes the **increase of side effects, toxicity and even of mortality,** determining at the same time the decrease of safety margins between **ED** and **LD_{50}**

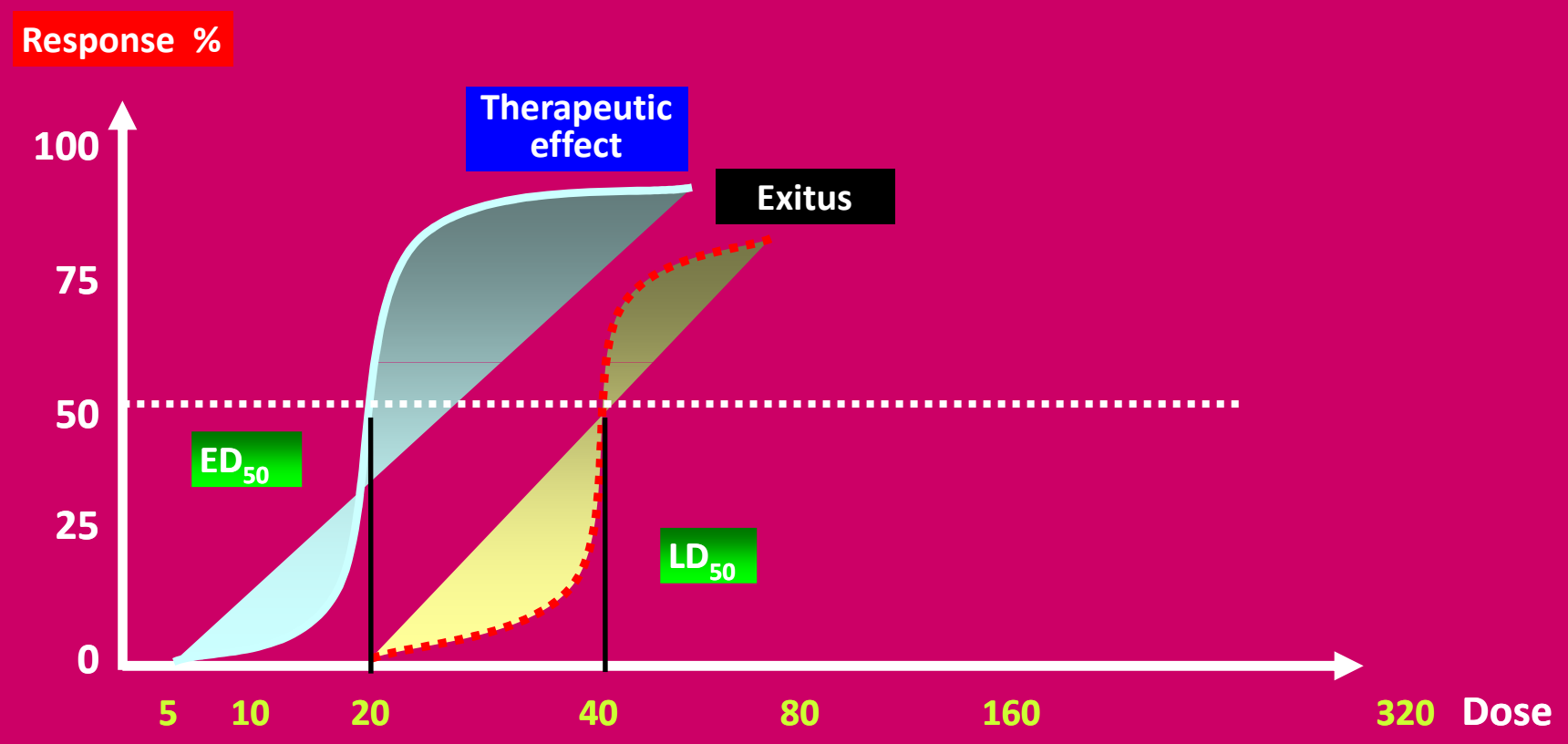
The higher the difference between ED and LD the safer the product will be .

The ratio between the dose that produces side effects and the dose that has therapeutic effect is called therapeutic index (TI) or safety limit and indicates the selectivity of a drug.

$$T.I. = \frac{\text{Dose that produces side effects}}{\text{Dose that has therapeutic effect}}$$

A medication can have multiple TI if it has more side effects or more therapeutic effects.

The correct dosage is established by determining the safety limit and the relationship between the maximum therapeutic dose and the minimum dose that induces toxicity.



Graphical representation of ED_{50} and LD_{50} for a hypothetical drug which can be used in therapeutics due to a tolerable safety limit.

Pharmacokinetics of

administration and absorption

Most forms administered p.o. are solid formulations.

The substance released from the excipient → diffuses → crosses the G. I. and hepatic barrier → into the portal vein.

The degree of drug stability in contact with enzymes will significantly affect the amount of drug that reaches the systemic circulation.

For example:

- amoxicillinline will be absorbed 60-70%,
- ampicillin 20-40%,
- neomycin 3-6%

The difference between the pH of plasma and the pH of the g.i. tract plays a role in the absorption of p.o. drugs.

Example:

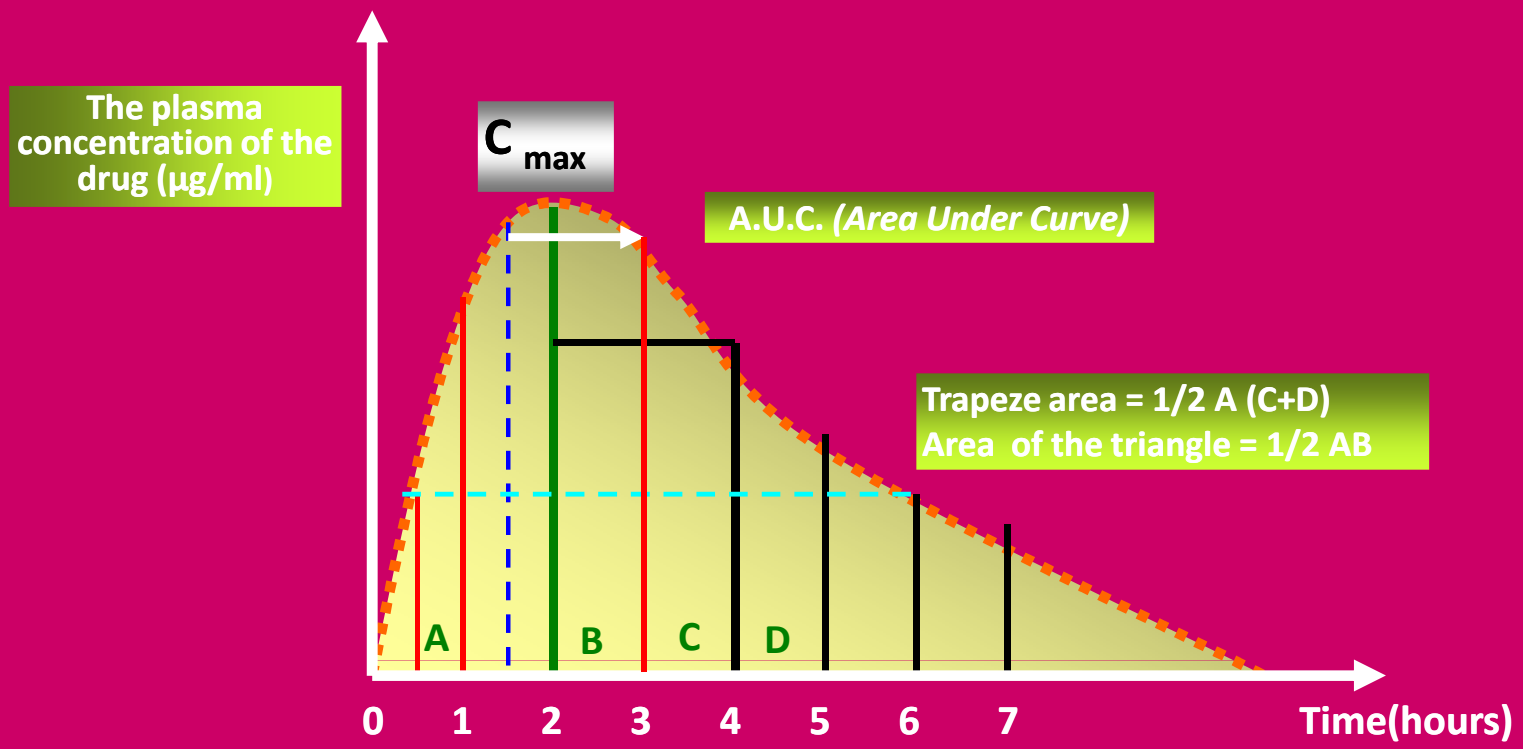
gastrointestinal pH by species is:

horse = 5,5,

dog = 2,5-3 and

pig = 3-4.

- An important physiologic factor in drug absobtion is the rate of digestive tract evacuation.
- Microorganisms from the digestive tract can be destroyed by drugs = decreased digestion and slow evacuation of the digestive tract.
- In ruminants at a pH of 5,5-6,5 appears in the digestive compartments a phenomena of microbial fermentation.
- Drugs (especially antibiotics), will inactivate the microflora, with direct consequences on the emptying rate of the gastric compartments.
- Quantifying the absorption is based on the plasma concentration (Pc) of the drug, and the graphical representation is shown in the figure below.



A. **The rate of absorption** - is the time necessary for one half (T1 / 2) of the administered dose to be absorbed and found in the systemic circulation.

B. **The level of absorption (bioavailability)** - represents the extent to which a drug administered in a particular dose enters the systemic circulation unchanged (as active form).

$$BD = \frac{AUC_{oral}}{AUC_{IV}}$$

For the same drug bioavailability varies from individual to individual or from one species to another.

For example, in dogs orally administered drugs have different BD:

- digoxin cpr. - 1mg/animal = 80% systemic BD
- propanolol cpr. - 80mg/animal = 2-7% systemic BD
- lidocaine solution - 10mg/kgbw = 15% systemic BD

Bioavailability

of a.u.v. drugs

Of fundamental importance are the issues related to the *influence that a formulation has on the action of active substances.*

In the last period of time, an increasing importance is given to the notion of: *biological bioavailability.*

This biological bioavailability is related to knowing the changes that drugs suffer within the body and is expressed as a percentage following the relationship:

$$\% \text{ availability} = \frac{S_1}{S_2}$$

where:

S_1=*blood levels obtained for the test preparation*

S_2=*the blood concentration of a reference preparation*

A pharmaceutical formulation must have a determined, predictable speed of action and be dependent on the variability of individual response.

Polymorphism:

The property of a substance to crystallize in different ways. Polymorphs have the same chemical properties, but different physical properties.

Crystalline polymorphism

The ability of a substance to *crystallize* in two or more crystalline forms *with a different spatial arrangement.*

Amorphous substances usually have small particles and can be found either in anhydrous form, or with crystallization water molecules.

For example:

The anhydrous substances of caffeine and theophylline have higher dissolution rate than the crystalline forms .

Therefore: ***the degree of solubility, hardness, configuration, dimensions, optical and electrical properties*** **etc. are different from one polymorph to another,** ***altering the biological availability.***

Hydrocortisone acetate **may exist** ***under five crystalline forms,*** **each with its own biological availability;**

Chloramphenicol, **under its forms palmitate and stearate, exists** ***in three*** **polymorphic** ***forms*****: two crystalline and one amorphous, the more active is the second crystalline form, otherwise the most common of chloramphenicol esters** (Leucuţa, 1975).

Other active substances (ex. acetyl salicylic acid, barbiturates, corticoids, sulfathiazole, steroid derivatives etc.) may be encountered under two or more crystalline forms, each with their own different speed of dissolution, therefore different absorbtion.

Designation of polymorphs

It is made with *roman numbers* (the digit I corresponding to the most stable form) or in *capital letters* (in order of their discovery).

***The thermodynamically unstable forms* are called *metastable*.**

These are preferred, because using forms with high solubility and energy constitutes an advantage.

For example,

Novobiocine (amorphous, acide form) can not be processed in suspension, because in less than six months, at room temperature turns into crystallized form.

Particle size

For some substances with low solubility, the size of the particle determines gastrointestinal absorption, therefore, therapeutic efficacy (directly proportional to the logarithm of the particle surface area)(Leucuţa, 1975).

For example:

Particles of griseofulvin, sulfur, cortisone (prednisolone, medroxyprogesterone), sulfadiazine, barbiturates (finely pulverized).

Sometimes it is required the use of particles with different sizes in order to achieve optimal activity (reduced side effects, eliminate intolerance, maximum effect).

Particle size

Influences directly the activity of drugs that are administered parenterally as suspensions (ex. penicillins, testosterone esters).

Particle size, in these cases is between 1-20μm and are *micronized powders* composed of very small particles (monoparticles).

It has been found that *the tolerability of a drug* is closely related to the size of the particle.

For example:

Aspirin administered in monoparticles causes less gastric bleeding than in the form of large particles.

Nitrofurantoin in the form of small crystals easily causes side effects (vertigo, nausea), than larger particles (that are absorbed more difficult).

That is why, in this case, the optimum size (to avoid a fast dissolution) is 50-100 μm.

For a complete action of some digestive antiseptics and antihelmintics, they should not have a rapid dissolution, that is why, the most effective particles are de 100μm (Leucuţa, 1975).

Determination of the particle size

Must take into account not only the aspects of the pharmaceutical technique, but also the pharmacological implications.

It is important in the case of some pharmaceutical forms (ex. powders, tablets, dragees, suspensions, suppositories, ointments) because it helps to establish measurement methods and the permitted particle limits for each drug substance.

Bioequivalence

of a.u.v. drugs

Two drugs are bioequivalent when they produce the same therapeutic effect and have the same rate and extent of absorption.

Bioequivalence of drugs

compares a drug with another or with a set of predefined quality requirements, including:

- ***chemical bioequivalence***

  ***the amount of active substance in two / more preparations*;**

- ***clinical bioequivalence***

  two preparations containing the same active substance give *identical answers*, measured through a pharmacological response or appreciated by controlling a symptom or a disease

- ***therapeutic bioequivalence***

  structurally *different* drugs, give the *same* clinical outcome;

Bioequivalence

two preparations containing *the same drug substance* in equal amounts allow the *passage* into the general circulation, at the *same* relative speed of the active substance, achieving *the same blood concentration*

From the biopharmaceutical standpoint, interest is shown in :

- ***selection of chemical status* (acid, base, salt, ether, ester etc.);**
- ***choice of physical state* (amorphous, crystalline, polymorph, hydrated, the particle size);**
- ***choice of pharmaceutical form* (liquid, soft, solid);**
- ***choice of adjuvants* (solvents, diluents, thickening agents, disintegrants, antioxidants, antiseptics, etc.);**
- ***choosing a suitable pharmaceutical technique*.**

The purity of the active substance

The impurities tolerated will *vary* depending on the: type of substance , origin and destination.

Therefore:

organic substances of synthetic origin are considered satisfactory, compatible with therapeutic use, if impurities do not exceed 0,5-1%, because the variability of responses in the body is sufficiently broad to compensate for small percentages of impurities.

The condition is valid when the impurities are biologically inert.

Some weak bases (alkaloids) or some acids (barbiturates), to turn into products with higher solubility will be converted into salts, through the so-called *salification with inert ions*.

So, election of the form must be made depending on the induced effect.

Therefore:

phenobarbital administered p.o., will be absorbed more slowly than its sodium salt (observed in almost all barbiturates);

polymyxin sulfate is more toxic than the metasulfonate, because of the gastric acidity that is produced (fine precipitate appears, well dissolved which allows a more rapid absorption) (Leucuţa, 1995).

In many cases, significant differences were found between the effect of the salified form, compared to the nonsalified form.

The pharmaceutical form

the use of substances as such is extremely rare, a drug formulation is composed in addition to the active substance also by supporting materials (solvents, emulsifiers, antioxidants, correctors, preservatives, dyes, thickeners, etc)

By definition, they should be inactive, biologically inert and should not produce physicochemical changes, harmful to the active substances.

This is *only theoretical,* supporting substances having a role in modifying drug absorption (either increasing or decreasing the speed of absorption), additionally claiming knowledge of the pharmacological effects of adjuvants.

For exemple:

Excipients of dermatological preparations, can influence the *degree of* i.d. *penetration* of the a.s.

surfactants (complexed of hydrophilic solvents, PEG), used to realize a suitable pharmaceutical form develop *solubilized drug systems* (poorly soluble before) *thus favoring absorption.*

This substances (often used as solubilizers and emulsifiers) act, generally, in three ways:

1). *moistening*

in low concentrations, surfactants lower the surface tension.

The effect occurs within the biophysical system (solid / liquid) consisting of the drug found in the GI fluids and will determine the passage of the poorly soluble substances into solution.

Also, certain surfactants improve absorption of drugs administered as :

eye drops, erin, suppositories or ointments.

2. *complexation*

In high concentrations, surfactants form complexes between drugs with lipophilic character. This phenomenon has been reported in case of associating antiseptic surfactants.

3. the *influence on physiological processes*

certain surfactants can affect physiological processes, of which the most important are:

- ***modification of cell permeability,***
- ***inhibition of gastric activity or***
- ***stomach evacuation delay.***

Working technique

Influences, the biological availability of a product.

It has been found that *different batches* of the same drug have different characteristics, this is due especially to changes, at least insignificant, usually hard to spot) of the working conditions.

For example:

tablets and dragees because of these "small" changes do not disintegrate in time, missing the drug release.

When it comes to instability one can speak of a chemical degradation of the active substance, accompanied by reduced activity, by a change of the drug that ceases the release of the active principle or, destructive change in the characteristics of the drug.

A task of the formulation and of the working tehnique is the realization of preparations which maintain their quality for a long period of time.

This is not an easy problem because the studied factors (temperature, light, humidity, air, microorganisms) cause unpredictable interactions.

Due to bioavailability, manufacturers determine *the most appropriate form* of administration, which corresponds not only medically (route of administration and dosage), but also from the point of view of biological activity, according to the individual parameters: age, sex, disease, route of administration etc.).

There are differences between monogastric and polygastric animals.

For example:

Salicylate administered p.o. in gelatin capsules to different species in doses of : 18,5; 50 and respectively 133mg/kgc in: dogs, pigs, ponies and goats indicated that BA is :

- very high in: dogs and pigs, while
- very low in: goats and especially in ponies.

2. Practical

elements of veterinary therapeutics

The choice of a rational therapy is not possible without an accurate diagnosis.

In this context, rational drug therapy must take into account :

- drug formulation,
- dosage scheme,
- the safety limit (IT),
- counter-indications,
- side effects,
- drug interactions, but also
- the associations of good nature.

Drug formulations :

► **with protected label**

belong to pharmaceutical companies which hold the license of manufacturing and can not be copied by other companies;

► **with generic name**

of which the patent has expired and can be produced also by other companies;

► **used off-label (Extra label)**

at doctor`s advice (which has responsibility!) a drug can be used outside the manufacturer's indications;

- **for human use**

  which can be used a.u.v., on the responsibility of the veterinarian and only for species whose products and by-products are not for human consumption;

- **unregistered**

  used on the risk of the clinician and owner (drugs in clinical testing).

- **prohibited**

  which are prohibited to be used in certain species or for all.

- In veterinary practice is common the situation where the sick animal is administered two or more drug substances, either separately or associated in the same pharmaceutical form.
- The higher is the number of concomitantly administered substances, the higher will be the risk of incompatibility.
- In case of interactions and incompatibilities, the effect they have on the animal may be manifested through:
  - mutual annihilation (total or partial) or decrease of the effect of associated substances and also installation of treatment failure;
  - negative effects on the animal manifested by deterioration or worsening of the general condition, and sometimes death of the animal by the appearance of toxic products.

Interactions and incompatibilities may occur before the drugs enter into the organism and are due to physicochemical phenomena, such as:

- precipitation,
- hydrolysis,
- liquefaction,
- effervescence,
- oxidation etc.

These interactions are common with i.m. injectable solutions, or in the case of intravenous infusion preparation .

In this context we must recall some essential terms:

1. Affinity
2. Efficacy
3. Potential

Drug associations

Drug associations

influence the pharmacodynamic effects through interactions.

Drugs may be associated in a single preparation or administered separately.

Through associations we seek:

- enhancing the action of a drug,
- extending the action of a drug,
- reduction / cancellation of the action of an association ,

The pharmacodynamic interactions can be:

- Synergistic, when the drugs act in the same way (ex. lincomycin + spectinomycin → mycoplasma).
- Antagonistic, when the drugs act contrary (ex. effects of histamine / antihistamine).

Synergistic interactions

can be classified into two categories :

Addition

effects of two or more drugs are summed (ex. antiinflammatory analgesics + antipyretic).

Potentiation

the global effect is greater than the sum of partial effects

Example:

lincomycin → Gram positive and Mycoplasma;

spectinomycin → Gram-negative, and Mycoplasma;

lincomycin + spectinomycin → Gram positive, Gram negative, and Mycoplasma

Antagonistic interactions can be :

Partial

when the global effect is smaller than the partial effects

Example:

- non-steroidal anti-inflammatory + diuretics,
- heparin + aspirin etc.

Total

when the global effect is null

Example:

- atropine + pilocarpine

Drug interactions

- **Drug interactions** = changes in the nature and intensity of the therapeutic response to a drug compared to another drug administered at a time or simultaneously, in an animal.
- **The resultant of the interaction** = either increase or decrease of an a.s. or a specific metabolite, at the site of the biologic action, called: **pharmacokinetic interactions** or those installed by other mechanisms = **pharmacodynamic interactions.**
- **"Physiological type"** incompatibilities are the result of proper or improper association of active substances that are used therapeutically (or diverted from the desired effect).
- Generally this type of incompatibilities belong to the veterinarian who, inadvertently or by ignorance, causes them. (from here the word iatropathy: **iathros = therapist, pathos = distress**).

Pharmacodynamic incompatibilities are connected to the pharmacodynamic action produced by the drug.

They are divided into those that occur :

- **outside the body** (therapeutic technique)
- **inside the body :**

- changes in the **pharmacokinetic parameters** determined by the **presence of another** medicinal **product**;

- alterations of **pharmacodynamics**, due to the presence of **another medicinal product.**

Pharmacokinetic

interactions

- The pharmacokinetics of a drug can be modified at all levels: absorption, distribution, metabolism, excretion, with implications related to therapeutic efficacy (by influencing the availability of the substance at the site of action).
- associated drugs may alter the pharmacokinetic behaviour of each other in the processes of absorption, distribution, metabolism and excretion.
- Changes can lead to:

  - decrease of therapeutic efficacy or

  - the occurrence of side effects,

  because the changes affect the availability of the substance at the site of action.

- Pharmacokinetic interactions which determine modification of availability at the site of action are generally driven by decrease in the rate of absorption or by increased rate of metabolism or excretion

- Increased bioavailability in the biophase may be determined by pharmacokinetic interactions like:

  - protein coupling rate modifications,

  - blocking the metabolism or

  - blocking the renal excretion (Leucuţa, 1976).

a. Interactions on absorption

The mechanisms by which these processes become viable are:

- movement of the drugs from the plasma protein binding sites;
- enzymatic induction / inhibition (change of biotransformation).

▼

Resulting = modification of half-life($t_{1/2}$).

Gastrointestinal absorption of a drug may be accelerated by the intervention of a second drug

Example:

phenacetin, paracetamol, vitamin B_{12} will be absorbed more rapidly in the presence of sorbitol,

epinephrine administered i.m. in combination with a local anesthetic will extend its absorption by local vasoconstrictor effect.

Influence of the digestive tract on absorbtion

In the intestine,

Metal and salt molecules (ex: Ca^{+2}, Mg^{+2}, Al^{+3}, Fe^{+3}) produce, in the presence of other drugs, poorly soluble complex combinations thereby, poorly absorptive (ex: powder tetracycline administered in milk or feeding the young simultaneously with milk; this drawback can be removed by distancing milk administrations to 2-3h after drug administration).

- Simultaneous administration of tetracycline with preparations based on aluminum hydroxide (ex. antacids, digestive bandages) determines the decrease of plasma level of tetracyclines (even 90%), due to formation of chelates.
- Administration of anions with increased affinity for acid molecules may influence the absorption, especially of: fat, thyroid hormones, cardiac glycosides, iron salts, warfarin, phenylbutazone, vitamins A, D, E, K, etc.).
- Anticholinergics and opiates delay gastric emptying, significantly slowing the absorption of other p.o. drugs
- Due to alteration of peristalsis, may delay the dissolution of some tablets.

- Due to prolonged stationing in the intestine, some drugs can absorb incorrectly

  Example:
- Metoclopramide (stimulator of gastric emptying), increases the absorbtion of paracetamol but decreases the gastric concentration of digoxin.
- Neostigmine (anticholinesterase) alters the rate of absorbtion in many drugs with whom is associated, due to stimulation of intestinal peristalsis.
- Barbiturates (phenobarbital) decrease the antifungal effect of griseofulvin.
- Saline purgatives decrease the absorption by diluting the intestinal contents and accelerating the transit.
- The intestinal flora modifies the activity of several active substances, due to biochemical changes that take place.

- Antibiotics may act directly on the intestinal flora and thus indirectly, modify the plasma concentrations of other drugs.

  Example:

  Increasing the effect of anticoagulants by destroying the flora that produces vitamin K in concomitant administrations of chloramphenicol, neomycin, oral sulphonamides and penicillin derivatives.

  Simultaneous administration of broad-spectrum antibiotics in some cases can cause enteritis (and therefore, due to reduced absorption, decrease in the effect of anticoagulants).

- The enzymes can also be inhibited by drugs:

  - folic acid absorption occurs in the presence of glutamate (originating from food) that results from hydrolysis.

  Diphenylhydantoin or nitrofurantoine may prevent this hydrolysis, resulting: the decrease of folic acid absorption rates.

- Associations with adsorbents (ex: activated charcoal, kaolin, bentonite, powdered liquorice etc.) or mucilage can determine physicochemical interactions, which will delay the absorption due to retention of active principles on their molecules and their gradual disposal

  Example:

  - kaolin reduces the absorption of lincomycin;

  - cationic antacids decrease absorption of tetracyclines,

  - surface-active agents increase poorly soluble drug toxicity, by solubilization.

- In the case of parenteral administration are possible interactions that are useful in therapeutics.

- **Subcutaneous medications** will be absorbed more quickly in association with vasodilator drugs or by the addition of substances that **increase the permeability of connective tissue**(ex: hyaluronidase).
- **Delay of the absorption rate** in drugs that are administered s.c. or i.m. is achieved by combination with heavy absorbable macromolecular substances (ex: PVP) or with vasoconstrictors (ex: adrenaline, procaine).
- Some **drug interactions** may decrease the permeability of connective tissue

  Example:

  Estrogens can increase the level of hyaluronic acid in the fundamental substance and thus will **decrease the rate of absorption** of the associated drugs.

Influence of pH

Digestive and intestinal juices may influence absorption in an unpredictable manner through pH.

There are several mechanisms by which the absorption is affected:

Variations in pH of the gastric and intestinal juice = alkalizing substances that decrease the absorption of weak acid drugs.

Formation of complexes

- Tetracyclines form reversible or ireversible chelated complexes, with metal ions (especially: calcium, aluminium, iron);
- Furosemide forms a non-resorbable complex with magnesium hydroxide.

Modification of the gastrointestinal motility

There are drugs that accelerate the G.I. transit,decreasing absorbtion (metoclopramide, sodium bicarbonate) or delay the intestinal transit (atropine, morphine analgesics, aluminium hydroxide and magnesium).

Competition for the same transport system.

In case of associations between substances which are transported by the same membrane active transport system, these get in competition for the binding sites on the transporting plama proteins.

Through saturation of these sites may occur a mutual reduction of absorption of the attached substances at this level (ex. phenytoin prevents absorption of folic acid).

Influence on the intestinal metabolization

Intestinal enzymes can metabolize drugs, for example chlorpromazine, which is metabolized 50% at this level.

Impairment of intestinal blood flow

There are substances with high fat solubility which quickly cross the intestinal barrier , in this case the blood flow at the intestinal level becomes a limiting factor of absorption, when combined with a product that decreases or increases intestinal blood flow, absorbtion may decrease or increase.

Toxic effects on the digestive tract

The drugs or the duration of their administration may lead to toxic phenomena or malabsorption.

Ex. Neomicine p.o. on long term administration = atrophy of the intestinal villi = malabsorption.

b. Interactions on the distribution

Interactions in the phase of coupling

If a drug is highly bound to plasma proteins, then its displacement by an associated drug substance, capable to displace it competitively, leads to an increase of the free concentration of the first drug substance.

The result: potentiation of the effect, due to the fact that, the unbound free fraction is the one that has pharmacokinetic action (because accesses the pharmacoreceptors).

- Phenylbutazone and sulphaphenazol displace tolbutamide from the plasma proteins, inhibiting its metabolism (leading to hypoglycaemia).
- Valproic acid lowers the plasma level of phenytoin by displacing it from the protein and speeding up the metabolism of the free fraction.
- Therefore, for that medicinal products to be involved in interactions of displacement from protein (in such a way that the displace to be clinically significant) they must possess, in addition to a high protein binding, a reduced apparent volume of distribution (Vd) and a low therapeutic index.

- The affinity for plasma proteins can be modiffied by binding another drug.
- Aspirin, besides the fact that is reversibly bound to serum albumin, also acetylates it . Acetylated albumin will present high affinity for phenylbutazone (and a lower fenfenamic affinity).
- In this way, it is possible for the effect of such an interaction to manifest long after a substance that produced it was eliminated (in this case aspirin).
- Reversible fixation is a condition for drug action, ireversible binding causing toxic action.

Distribution ratio in different organs and tissues (Synthesis, Cristina)

Organ / tissues	Horse	Dog	Goat	Cow	Human
Blood	8,60	-	4,70	7,80	-
Brain	0,21	0,51	0,29	0,06	2,00
Heart	0,66	0,82	0,48	0,37	0,47
Lung	0,89	0,89	0,88	0,71	1,40
Liver	1,30	2,32	0,95	1,22	2,60
Spleen	1,11	0,26	0,25	0,16	0,26
Kidneys	0,36	0,61	0,35	0,24	0,44
Intestine	5,80	3,90	6,40	3,80	1,70
Intestinal content	12,30	0,72	13,90	18,40	1,40
Skin	7,45	9,30	9,20	8,30	3,70
Muscle	40,10	54,50	45,50	38,50	40,00
Bones	14,60	8,70	6,30	12,70	14,00
Tendons	1,71	-	-	-	2,00
Adipose tissue	5,10	-	-	18,09	18,10
Average weight	380,0	16,0	39,0	620,0	70,0

Changes in blood flow

at hepatic levels **affect the bioavailability of** certain medicinal substances metabolised by the liver (noradrenaline administered i.v. decreases hepatic clearance of lidocaine).

Displacement from plasma proteins

Competition becomes critical when the binding sites on the protein macromolecule become **almost saturated.**

Example:

- phenylbutazone → oral anticoagulants;
- Non-steroidal anti-inflammatory drugs → antidiabetic sulphonamides;
- antibacterial sulphonamides → oral anticoagulants.

Therapeutic plasma concentration will depend on:

- the size of the dose
- interval between administrations
- dosage form
- administration route
- systemic distribution
- rate of absorbtion
- degree of absorbtion
- degree of plasma protein binding
- rate of elimination

Binding to plasma proteins has a role in limiting the distribution and influences drug elimination .

The link is reversible, constituting a reservoir of active substance (when releasing the specific receptors).

Example:

Ceftiofur is metabolized in desfluorilceftiofur, the latter having a high binding affinity to plasma proteins, causing the increase of $T_{1/2}$ from 1 hour to 10 hours.

hypoalbuminemia (nephrotic syndrome) = increasing the amount of free plasmatic drug (more than 80% for phenilbutazone, furosemide, ceftiofur).

c. Interactions on metabolization

Interactions by enzyme induction

Enzyme induction causes:

- increased clearance and
- decreased plasma concentrations of drugs.

The consequence of the enzymatic induction is manifested by reduction or cancellation of therapeutic effects.

Interactions by enzymatic inhibition

some drugs can inhibit the metabolising enzymes: chloramphenicol, phenylbutazone, estrogens, imidazoles, some sulphonamides and therefore, the hepatic clearance is reduced and increases the concentration of substances that would have been metabolized under the action of those enzymes.

The drugs can also influence the metabolism of endogenous substances (ex: bilirubin, steroid hormones etc.).

	Inductor	Medicament(e) sau substanţa(e) a(ale) căror metabolism este stimulat
Drugs that stimulate biotransformation of other drugs or substances (after Safta, 1984)	Fenobarbital şi alte barbiturice	Derivaţii ac. salicilic, fenazona, aminofenazona, fenilbutazona, barbiturice, fenitoina, clorpromazina, dismetilimipramina, anticoagulante de sinteză (indirecte), digitoxina, digoxina, testosteron, androsteron, estradiol, progesteron, anticoncepţionale orale, hidrocortizon, dexametazona, tiroxina, chinina, cloramfenicol, doxicilina, griseofulvina, ciclofosfamida, bilirubina
	Fenitoina	Fenazona, corticosteroizi, hormoni sexuali, tiroxina, anticoagulante indirecte, digitoxina, doxicilina, vitamina D
	Fenilbutazona	Corticoizi, hormoni sexuali, aminofenazona, digitoxina, digoxina
	Fenazona	Anticoagulante indirecte, hormoni steroizi
	Fenotiazinele	Anticoagulante indirecte, benzipren
	Haloperidol	Anticoagulante indirecte, benzipren
	Meprobamat	Meprobamat, anticoagulante indirecte
	Diazepam	Diazepam
	Clorciclizina	Hormoni steroizi
	Prometazina	Fenilbutazona
	Prednison	Fenilbutazona, ciclofosfamida
	Tolbutamida	Fenilbutazona
	Spironolactona	Fenazona, anticoagulante indirecte, hexobarbital, cortisol
	Rifampicina	Rifampicina, fenazona, tolbutamida, hexobarbital, metadona, digitoxina, anticoagulante de sinteză, hormoni steroizi
	Griseofulvina	Anticoagulante de sinteză
	DDT	Corticosteroizi, hormoni sexuali, tiroxina

Enzymatic inductors also stimulate microsomal oxygenase systems:

- NADPH-cytochrome P-450 reductase,
- cytochrome P-450,
- UDP-glucuronyltransferase and
- glucose-6-phosphate dehydrogenase.

Non-specific inducers can stimulate their own metabolism or the metabolism of other chemical compounds.

From the category of nonspecific inducers we can mention:

phenobarbital, glutethimide, meprobamate, hexobarbital, pentobarbital, carbamazepine, phenytoin, ethanol, chlorpromazine, tricyclic antidepressants, phenylbutazone, aminophenazone chlorcyclizine, tolbutamide, probenecid, halothane, rifampicin, DDT etc.

Inhibition of drug metabolism

Leads to an extension and exaggeration of the pharmacodynamic effect and/ or to the occurrence of adverse effects.

Inhibition of enzymes involved in the biotransformation may determine, especially inhibition of their activity or their synthesis.

The interactions affect hepatic microsomal enzymes, with the possibility of interaction with other enzyme systems.

Blocking enzymatic synthesis = less common as induction

Drug interactions often determine inhibition by competition, for the same enzyme system.

Interaction through inhibition of biotransformation of drugs and clinical consequences in animals
(after Safta, 1984)

Medicament cu metabolismul inhibat	Inhibitor	Consecinţe
Fenitoina	Anticoagulante indirecte, PAS, Cicloserină, Fenilbutazona, Clorpromazina, Diazepam, Halotan, Carbamazepin, Estrogeni, Sulfafenazona	Tulburări neurologice Hiperplazie gingivală
Bishidroxicumarina	Cloramfenicol, Feniramidol, Fenilbutazona, Oxifenilbutazona, Clorpropamida, Chinidina, Etanol, Steroizi anabolizanţi	Accidente hemoragice
Tolbutamida	Cloramfenicol, Fenilbutazona Probenecid, Salicilaţi Paracetamol, Sulfafenazol Anticoagulante indirecte	Hipoglicemie
Clorpropamida	Cloramfenicol, Dicumarol	Hipoglicemie
Hexobarbital	Ac. aminosalicilic, Testosteron, Progesteron, Hidrocortizon	Prelungirea acţiunii
Fenobarbital	Fenitoina	Diverse reacţii adverse
Promazina	Dietilstibestrol Progesteron	Prelungirea efectului
Perfenazina	Nortriptilina	Prelungirea efectului
Fenazona	Fenilbitazona Ac. nalidixic	Prelungirea timpului de înjumătăţire
Fenilbutazona Oxifenilbutazona	Steroizi anabolizanţi	Prelungirea efectului Reacţii adverse
Etilmorfina	Estradiol	Prelungirea efectului
Ciclofosfamida	Cloramfenicol Prednison	Diminuarea efectului Reacţii adverse

d. Interactions on urinary excretion

The excretion of the drug is linked to the:

- glomerular filtration,
- tubular reabsorption and
- tubular secretion.

Many pharmacons are eliminated through several mechanisms.

Free drugs, unfixed on plasma protein:

► are eliminated through glomerular filtration.

Ultrafiltration can be/or not followed by tubular resorption

Unionized, liposoluble forms of drugs can be reabsorbed by the membrane of the renal tubules.

An important factor that intervenes in directing resorption is the pH of the tubular urine:

· in acid urine, weak acid drugs are under unionized liposoluble (HX) form, which diffuses easily from the renal tubule towards the plasma, having a low-clearance;

· in alkaline urine, they are under ionized, nondiffusible form (X- + H+), which is excreted in urine.

In the case of weak alkaline drugs, the situation is the opposite.

Urine pH may vary, with values of 4,5 - 8, its changes considerably influences the tubular resorption and, consecutively, the renal excretion of drugs.

In the case of drugs that are weak acids (pKa 3-7) (ex: anticoagulants, nalidixic acid, barbiturates, indomethacin, phenylbutazone, salicylates, streptomycin, sulfonamides, penicillin etc.) excretion will decrease if the urine is acidic and will increase if the urine becomes alkaline.

Drugs that are weak bases (pKa 7,5-10,5) (ex: caffeine, antihistamines, antipyrine, nicotine, pethidine, procaine, theophylline, etc.) show an increased urinary excretion in the case of acid urine. In alkaline urine, their elimination decreases (Safta, 1984).

- From the drugs that may lead to changes in the urinary pH, we mention: sodium bicarbonate, which alkalinizes urine, as well as ascorbic acid and ammonium chloride, which produces acidification of urine.
- Urine alkalinisation is necessary when administering sulphonamides, which acetylate (ex: sulfathiazole, sulfadiazine etc.) to avoid intratubular crystallisation.
- In urine with an alkaline pH, the solubility of sulphonamides is increased.

Drug interactions at the level of the active transport systems in the renal tubules
(after Safta, 1984)

Medicament	Interacţionează cu:
Sulfamide	Penicilina G, Tolbutamida
Probenecid	Penicilina G, Ampicilina Oxacilina, Carbenicilina Cefalotina, Indometacina Clorotiazina
Salicilaţi	Probenecid, Fenilbutazona Sulfinpirazona, Penicilina Metotrexat
Fenilbutazona	Penicilina G, Tolbutamida Acetohexamida
Oxifenilbutazona	Penicilina G
Aminofenazona	Penicilina
Derivaţi cumarinici	Clorpropamida
Sulfinpirazona	Salicilaţi

Influence of pH on absorbtion, distribution and elimination of certain drugs
(after Safta, 1984)

Procesul	**Medicamente acizi slabi**	**Medicamente baze slabe**
Absorbţia gastrică	relativ rapidă	relativ lentă
Absorbţia în intestinul subţire	relativ lentă	relativ rapidă
Raportul concentraţie plasmatică / concentraţie intracelulară	Ridicat	scăzut
Clearance renal în: - urina acidă - urina alcalină	 - redus - ridicat	 - ridicat - redus

Interactions

of pharmacodynamic order

A **pharmacodynamic effect**(sin. pharmacological action)

The sum of the body's responses reflected functionally, after administration of drugs.

Body – drug interaction = **amplification** or **decrease** of some specific functions of the organism with (generally) reversible character, that does **not** result in the creation **of new** physiological **functions**.

The occurence **of a "visible" effect** = linked to the existence of a minimum dose of the drug.

Main effect

The most visible response that occurs after the administration of a drug (ex: narcosis after administration of a narcotic, healing a bacteriosis after treatment with an antibiotic etc.).

Secondary effect

less intense response or responses that can accompany a main effect (ex: the sedative effect, even hypnotic of antihistamines).

Generally, the secondary effects are not wanted in the practice of veterinary therapy, they being harmful (adverse reactions)

Another classification refers to the functional changes that a drug determines in the body:

Stimulating effect

when a drug increases the functional status of an organ, apparatus or system :

- direct, through excitatory stimuli directed towards these or
- indirect, by blocking or reducing an inhibitory function

Example:

- adrenaline stimulates beta-adrenergic cardiac receptors = tachycardia, change that can also be achieved by inhibiting M-cholinergic cardiac receptors by atropine).

- Digitaline can stimulate the myocardium (stimulating activity) but at the same time, may decrease the conductivity of Hiss bundles (therefore inhibitory activity).

Depressing effect

Realized by drugs that have the ability to reduce the operational state of an organ, apparatus or system by actual inhibition or by excitation of an inhibitory function:

Example:

Paralysis of adrenergic catecholamine endings (tachycardia) is achieved directly through administration of guanethidine.

physiological result = bradycardia.

At the same time, acetylcholine can achieve the same effect indirectly through the excitation of M-cholinergic cardiac receptors (bradycardic role).

Some drugs can cause depressant effects, that will abolish (paralyze) the targeted function.

This medication is used when in practice is found the exaggeration of some functions during some diseases (ex: CNS depressant substances, in the case of an abnormal excitation, antispasmodic substances, antidiarrheals, astringents etc.).

Related to this classification, physiological changes can be expressed through:

Direct effect

The active substance acts on the target directly (ex: bulbar center excitation by CO2 or cortical nerve center excitation by caffeine);

Elective effect

When drugs act in a particular manner, electively, only on an organ or a function (ex: digitalics act electively on the heart and its function).

Actually, a few drugs possess this feature, the influence being also over other organs or systems of the body (ex: same digitalis = acts also on the CNS and kidney), therefore, one can not speak of an actual elective effect.

More accurate is the expression:

preponderant or dominant effect.

Indirect effect

characterized by induction of the same changes (as in direct action), but in a different manner.

Caffeine, can cause vasoconstriction by direct action, but may also cause “indirect vasoconstriction” by stimulating the bulbar vasomotor center.

So, caffeine reduces diuresis both through direct action (on the kidneys), and indirectly (action on the cardiovascular system).

A classification of the effects may relate to location :

Local effect

identifiable at the administration site and is considered not to reach the vascular bed.

The best known "producers" of local effects = topical medications.

This classification is purely theoretical, because topical medications have more than local effects, through interactions with the adjacent tissues.

General effect

Occurs once the penetration of the drugs in the general circulation is produced, which then, because of the distribution, determines effects in all tissues and organs.

Example:

- strychnine, triggers general effects, through excitation of the CNS,
- adrenaline, through its hypertensive action,
- papaverine, through its antispasmodic action.

Drugs with general action can act locally: ex. local irritant activity of chloralhydrate, (a narcotic).

Depending on the specific activity, antibacterial, anti-pathogenic or symptomatic, the effects can be :

Etiotropic effect

refers to the action of drugs on the pathogens (ex: chemotherapeutics, antibiotics, antiparasitic). In veterinary medicine etiotropic therapy is considered to be the most rational.

Anti-pathogenic effect

result of a drugs action on the installed pathogenic mechanisms of a disease.

Therefore, relates to other causes of a disease, different from the etiologic agents (ex: hypovitaminosis, hipomineralosis, histaminemia etc.) that are controlled through specific medication (vitamins, oligominerals, calcium, antihistamines etc.).

Symptomatic effect

Consecutively produced after a drug intervention on the symptoms of a disease.

The result = increases the body's resistance, even if the cause is not combated.

Example:

Caffeine prevents collaps → increases low blood presure,

Opiates suppress acute pain which can install shock.

Also symptomatic (indirect) effects → immunostimulants (tissular extracts, polidin, iodisept, vaccines etc.)

It is known that one drug can enter in relation with multiple types of receptors, their stimulation = diferent effects, sometimes opposite (ex: adrenaline produces vasodilatation in small doses by binding to beta receptors and vasoconstriction in therapeutic doses by binding to alfa receptors).

Synergistic combinations

Associations of "good nature“ = drug synergism.

Advantages:

- detectable therapeutic effect at low doses
- reduced incidence of adverse effects
- obtaining efficient conditionings

Disadvantages:

- potentiating effect with CNS depressant activity

Drug synergism (sin = together, ergon = action)

Has a direct practical importance because, through "thought associations", it can be obtained the same therapeutic effect but with much smaller doses, thus reducing the incidence of adverse reactions.

The synergism can be direct and is called summation (or addition).

Determines final effects (E) which can be at most, equal to the algebraic sum of the partial effects of two associated drugs, A and B (E < A+B).

Direct synergism

Is characteristic of active substances related as mode of action, which exercise their mechanism on the same "targets".

In this type of synergism (summation or addition) associated drugs do not affect each other, the rate of attachment on the receptors being equal.

Expanding the spectrum of activity → associations:

antibiotics: penicillin + streptomycin, ampicillin + cloxacillin, gentamicin + vancomycin or

antiparasitics: rafoxanid + thiabendazole, oxiclozamid + tetramisole, albendazole + levamisole etc.

If they do not have the same mechanism of action and have different morphological "targets", one speaks of indirect synergism (ex: pilocarpine and saline purgatives).

Drug potentiation

also a drug synergism but follows a final intensified effect, superior to the summ of partial effects caused by associated drugs A and B (E > A+B).

Potentiation is a super-addition of effects of some drugs from different therapeutic classes that may have similar effects (ex: association of sulphonamides + potentiators leads to increase x 5-10 times of the antibacterial activity,

Trifadoxin = Sulfadoxine + Trimethoprim in a ratio of 5:1 has an activity x 8-10 times stronger than each component.

Sulfaveridin = Sulfaquinoxaline + Etoxidiaveridin = amplified anticoccidian effect;

Magnesium sulfate potentiates the hypnotic action of chloral hydrate,

Penicillins are potentiated by some sulfonamides etc.).

Potentiation may also follow intensification of effects of a component of the association through another component of the association (this not having the same effect)

Example:

Neuroleptics potentiate narcotics:

Droperidol enhances fentanyl analgesia (in NLA).

Through potentiation, usual doses of a drug may be reduced, the effect of this combination is the same or broader

Example:

Therapeutic association between atropine and papaverine determines the same effect as the individual therapeutic doses, even at a 50% of the average therapeutic dose for atropine and 33% of the average therapeutic dose for papaverine).

Potentiating associations are very useful in veterinary medicine, clinical synergism being often required in the cases of veterinary therapy.

In conclusion,

potentiating associations can be the result of these mechanisms :

- inhibiting the inactivation of some drugs

  example: potentiate the activity of acetylcholine and choline esters by anticholinesterases;

- antagonize biosynthesis of a key component of the metabolism

  example: sulfonamides and potentializators inhibit microbial biosynthesis of tetrahydrofolic acid;

- sensitization of substrates to subsequent action of some drugs

  example: chlorpromazine causes changes in the CNS that will sensitize the neurons to the activity of some CNS inhibitors.

Attenuation associations

These are not very frequent in veterinary medicine, being used especially in the case of drugs with a "too drastic" action

Example:

Irritant and purgative activity of croton oil → diminished by sunflower oil (or castor oil), known to have a more "gentle" activity.

Indifferent associations

Made between drugs that do not influence each other. This associations → frequent in the case of magistral or standardized preparations.

Antagonistic associations

Antagonism

Is represented by contrary, opposite activity, of two or more drugs , which cancels partially or totally the pharmacodynamic action.

The situation requires the presence of an agonist (influencing the pharmacodynamic effect) and an antagonist (which influences the effect of the agonist, for the purposes of reducing or annihilating).

Antagonistic interactions

May occur in coupling on the cellular receptors or in different enzymatic proceses

Example:

Sulfonamides are competitively antagonized by PABA or by substances with similar structure which derive from this compound: procaine, anestezine;

Concomitant administration of a bacteriostatic and a bactericide is = drug antagonism.

Clinical drug antagonism can be classified as:

Direct

Two or more substances acting to the contrary, but on the same morphological objective

Example:

Circular muscles of the iris can be paralyzed by atropine, installing mydriasis, while eserine acts on the same muscles resulting its stimulation and the instalation, of miosis.

Indirect

Substances with contrary activity acting on different morphological objectives

Example:

Pilocarpine contracts the pupil by stimulating the circular muscle of the iris, while adrenaline dilates the pupil acting on the radial muscle of the iris.

Depending on the intensity of the pharmacodynamic action the antagonism is:

Unilateral

When one of the antagonist active substances has a **more intense** pharmacodynamic activity.

It is the most common situation in veterinary therapeutics (depressor substances usually have a stronger activity than the stimulants);

Bilateral

When antagonistic substances have the same **intense** activity.

These two types of antagonism are also called: physiologic or pharmacodynamic antagonism.

Also antagonism is the :

- physycal and
- chemical one,

Forms that occur from direct physical or chemical agonist-antagonist type of reaction.

Example:

EDTA, ability to fix heavy metals,

Acid + alkali in states of acidosis of the digestive tract,

Albumins in contact with salts of heavy metals,

Tannins in presence of alkaloids etc.

Pharmacodynamic ambivalence:

Two substances can be both synergistic and antagonistic:

Papaverine is:

→ synergistic with morphine when it comes to analgesia,

→ antagonistic on the digestive sphincters that morphine contracts, and papaverine relaxes them;

Narcotine and morphine are:

→ synergistic as activity on pain,

→ antagonistic in what regards the respiratory center, narcotine stimulates, and morphine depresses it.

The body as a "whole" receives "information" from the outside and inside, administration of drugs being a "stimulus" adjusted by feed-back.

When drugs "depress" the physiological systems, the dependent morphological substrates will adapt, in the first phase by enhancing the functionality

In case of administration suppression of the respective drug, the compensation mechanisms remain present.

Biological antagonism.

It can be subdivided in:

1. Competitive antagonism
2. Non-competitive antagonism
3. Functional antagonism
4. Physiological antagonism

1). Competitive antagonism

It occurs when the agonist and antagonist act on the same effector receptor.

Competitive antagonism is:

- specific,
- reversible and
- mutual.

Non-competitive antagonism

The antagonist will not be fixed on the same receptor like the agonist or will act on different areas of the receptor.

Example:

Excessive administration of corticosteroids leads to major depression of the adrenocortical → hypothalamo - hypophyseal depression = corticotropin depletion.

In assessing the drug-receptor relationship are essential:

- affinity and

- intrinsic activity (the "attraction" between receptor and drug as well as the ability of the stimulated receptor to determine the pharmacodynamic effects).

Non-competitive antagonism may lead to :

a. **Inhibition of stimulants.**

drugs with powerful nonspecific, blocking effect, inhibit the action of stimulant pharmacons for certain effects

Example:

- Papaverine antagonizes serotonin,
- Histamine or acetylcholine → contracted smooth muscle relaxation (myotropic mechanism) not at the level of specific receptors;
- Convulsant effect of strychnine can be counteracted by blocking motor nerves with local anesthetics or by blocking neuromuscular junctions with curarizants).

b. allosteric inhibition

changes taking place around the receptor (consecutive to which, its spatial conformation will change).

In this situation, the agonist will no longer act,or will not be able to produce only but a partial interaction of these with the receptors.

This inhibition takes place at enzymatic level

c. Covalent attachment.

type of non-competitive antagonism, fixation by strong (covalent) bonds to the pharmacological receptors.

These processes are broadly of irreversible nature (ex: anticholinesterases).

Functional antagonism

In this case, the agonist and the antagonist act on different receptors of the same organ

It is about the activity as an agonist, on different receptors, in contrar sense

Example:

interaction between bacteriostatic- bactericide groups:

- First group prevents bacterial multiplication,

-The second one interferes and prevents bacterial growth phase,

Histamine contracts the bronchial smooth muscles, while

Isoprenaline will relax (ß-adrenergic mechanism) the same muscles, acting on the same type of receptor (histaminergic).

Physiological antagonism

Different from the functional one because the agonists and antagonists act on different tissues.

Example:

Increased cardiac output can be counteracted by hypotensive substances, reducing peripheral resistance.

To remove the toxicity and the side effects of drugs (by overdose), recognition of the type of antagonism is very important, antagonism may evolve and cause incompatibilities of various types (pharmacodynamic, of administration etc.).

Undesired

reactions to medications

Occur due to the failure to comply with the general principles of therapeutics:

- inappropriate therapies;
- nonanalyzing the risk-benefit relationship;
- not monitoring therapeutic response;
- nonanalyzing the impact + effect of the disease/ pharmacodynamics and pharmacokinetics of drugs.

Undesirable effects may be:

- predictable or
- unpredictible.

Occur mainly in: young, old, obese, emaciated, pregnant animals, or with hepatic disease/nefropathy.

Classification of adverse reactions:

- Low (limited) efficacy;
- Secondary effects
- Extensions of the pharmacodynamic properties,
- Allergic reactions

They can not be anticipated and are not related to the size of the dose

Are manifested by:

- skin reactions,
- hemolytic anemia,
- anaphylactic reactions etc.

Toxic reactions

complex mechanisms which are not related to the pharmacological effect of the drug (amino glycosides - nephrotoxic);

Idiosyncratic reactions

Appear as therapeutic surprises in a small number of animals and generally have genetic substrate.

In case of occurrence of adverse reactions the following measures shoud be taken :

- maintaining vital functions
- continuing the treatment (when is possible)
- changing the drug (when required)
- ensure drug clearance
- administration of the antagonist drugs or antidotes
- ensuring hepatic and renal function

Adverse

reactions

Undesirable or even dangerous effects, consecutively triggered by an inappropriate posology, often accompanied by immune reaction

The frequency of AR is more reduced than in human medicine.

In animals, it is estimated that the frequency of adverse reactions is: 5-8%.

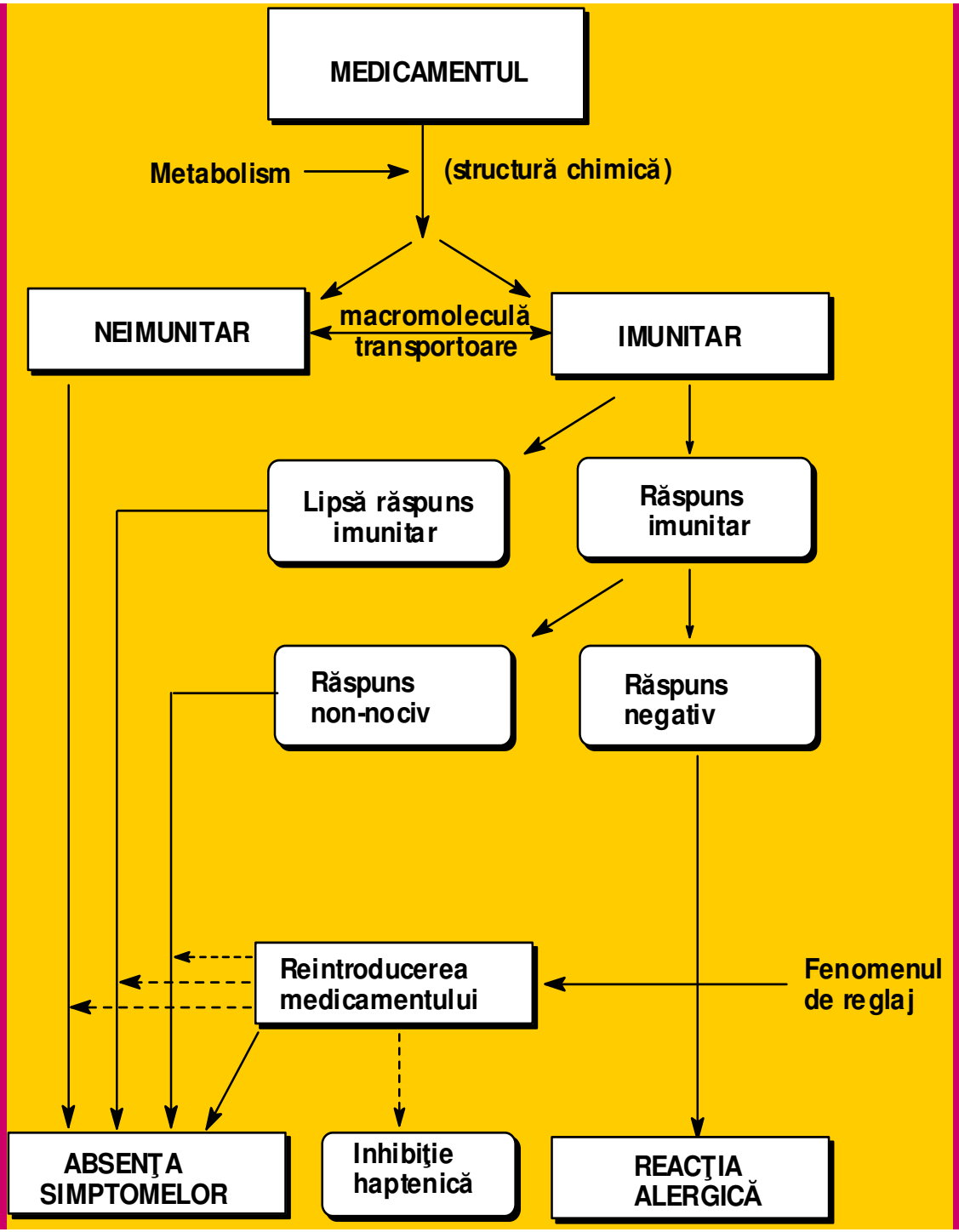
The most common adverse reactions are:

- toxic;
- idiosyncratic;
- allergic;
- mutagenic-teratogenic;
- carcinogenic.

Moreover:

In dogs, horses and cats have been identified tolerance type adverse reactions

In "custom" dogs and pigs, dependence type.



Immune response against a drug
(after Mihăilescu, 1980)

- **Toxic type adverse reactions**

Toxic reaction generally occurs:

- in the case of overdosing drugs with small chemotherapeutic index (ex: chemotherapeutics, anthelmintic, purgative, diuretic), which administered, often exceed the primary effect or

- may also be determined by **phenomenas that are not derived from the primary effect** (ex: auditory and vestibular organ damage by the aminoglycoside antibiotics) usually in products that appeared long ago on the market.

Example:

Florosil in pigs is not allowed to be administered in water or moist feed due to increased toxicity of fluorosil in water(1:25); santonin in parasitosis in pigs, etc.). Neguvon in p.o. administration in nematodosis in horses

An example of a toxic reaction = Herxheimer reaction = effect of endotoxins released by microorganisms, which die by the action of antibiotics. Generally bacterial metabolites are considered primary toxins, but these lead also to allergic sensitization.

H reaction can not be produced in the absence of bacterial infection and should not lead to abandonment of treatement with antibiotics.

If the likelihood of such reactions is anticipated, therapy should be started (contrary to usage) with low doses.

- Neurotoxic effects

Antibiotics can often be neurotoxic.

Example:

beta-lactams and polymyxins = hyperexcitation and convulsions.

Neurotoxic effects appear also at:

- acustico-vestibular level, as a result of damaging the eighth pair of cranial nervs, the vestibulo-cochlear, produced by streptomycin, kanamycin and neomycin, or at

- vestibular level, by: gentamicin, streptomycin and kanamycin.

polymyxins and chloramphenicols, affect the optic nerve, thus decreasing visual acuity.

arsanilic acid = neurotoxic effects on the optic nerve.

high doses of barbiturates (barbital, ciclobarbital, phenobarbital, pentobarbital, Inactin, Medinal etc.) = strong depressing activity on the CNS.

Butyrophenones (haloperidol, droperidol, azaperone)

- have a more intense action than phenothiazines regarding : hyperthermia and extra-pyramidal syndrome and
- potentiate barbiturates, narcotics and benzodiazepines.

Diphenylmethane tranquilizers (hydroxyzine, benactyzine):

- **depress** the respiratory centers in the CNS.
- **m-colinolytic action** (cardiovascular and digestive).
- **potentiate the activity of** barbiturates and opiates.

effects of hydroxyzine → amplified by phenothiazines.

Carbamate tranquilizers (ex. meprobamate)

- increase muscle relaxant activity and depress the CNS.
- depress the respiratory centers
- install paralysis of respiratory muscles,
- hypnotics are potentiated.

Benzodiazepines (Diazepam, Chlordiazepoxide)

- **CNS depressants,** and affect vision.
- **Potentiate the action of** CNS depressants, with serious evolution.

Amphetamines

- powerful CNS stimulants → prolonged use of high doses = installation of exhaustion after the end of the initial stimulation phase → depression of vital centers, due to lower functioning of the nervous cells.

- potentiate the activity of tricyclic antidepressants.

- induce pronounced adrenomimetic hypoactivity (x100 times lower, compared to adrenaline).

Purinic cortical stimulants (ex. caffeine, theobromine, theophylline)

- High doses affect CNS = excitation

Medullary and bulbar stimulants (ex. strychnine):

- **excite medullar reflectivity → lowering the excitability threshold = exaggerated responses (ex: seizures).**
- **blocks intercalar neurons in the control of responses.**

At the level of the bulb → depression of vital centers,

At the pripheral nerves→ curarizant type action (due to decrease of cronaxia).

- **Hematotoxic effects**

Antibiotics:

- in high doses = medulotoxic mechanism
- in low doses= hematotoxics

Example:

Chloramphenicol in high doses:

- depression of the spinal cord
- inhibition of hematopoiesis.

Hematotoxic disorders are recognized by:

- anemia (even aplastic) to: chloramphenicol[1], streptomycin,
- leukopenia to chloramphenicol and novobiocin,
- granulocytopenia and agranulocytosis to chloramphenicol and ristocetin
- thrombocytopenia to rifampicin and novobiocin.
- haemolysis may be determined by novobiocin and rifampicin.

[1] Chloramphenicol is already banned to veterinary use in farm animals in ROU.

Sulphonamides

haemolysant and methemoglobinisant, hematologic disorders = medular depression.

Frequent haematological disorders:

- **Leukopenia,**
- **Granulocytopenia**
- **thrombocytopenia, manifested clinically by severe anemia.**

Nitrofurans and furazolidone

- **hematotoxics (thrombocytopenia and agranulocytosis).**

Haemorrhagic diathesis → consecutive to using furazolidone in aviculture.

Benzodiazepines (eg. Diazepam, Chlordiazepoxide)

- **eosinophilia,**
- **anemia and**
- **thrombocytopenia.**

High doses of salicylic acid in dogs = anemia by suppressing erythropoiesis, hypotrombinemia and disorders of blood coagulation.

Following the destruction of the gastric mucosa = ulceration and haemorrhages.

Indirectly, histamine release = increase of acidity + local vasodilation.

Aspirin = coagulability disorders in newborns.

Phenacetin (paraaminophenolic derivative) = methemoglobinemia (aniline metabolites) → S-hemoglobin = haemolytic anemia.

- in enzyme deficient subjects (glucose-6-phosphate dehydrogenase):

methemoglobinemia, massive hemolysis, even exitus.

Paracetamol = phenacetin, but the methemoglobinisant action is 2-3 times lower.

phenylbutazone in excess = haemorrhages, reactivation of stomach ulcers, haematological disorders.

- **Dermatotoxic effects**

Sulphonamides after a long time use (1-2 weaks):

- intense pruritus,
- erythema,
- exfoliated dermatitis,
- angioneurotic oedema (especially petechial and purpuric) which,
- can give serious anaphylactic reactions.

Meprobamate, determines, in increased doses:

- Allergic manifestations.

Morphine determines

- eruptions, urticaria, pruritus.

Aspirin determines:

- hypersensitivity and skin reactions, oedema etc.

Aminophenazone and phenylbutazone produce, in increased doses:

Cutaneous allergic manifestations.

- **Hepatotoxic effects**

Antibiotics act hepatotoxic through mechanisms of:
- cytolysis (e.g. oxitetracyclines, clortetracyclines)
- steatosis (e.g. tetracyclines) or
- cholestatic (streptomycin, rifampicin, tetracycline).

Arsanilic acid,
A chemotherapeutic used in enteropathy in pigs and poultry
- Produces even at slightly increased therapeutic doses (300-400 mg/kg fodder) masive hepatotoxic effects.

chemotherapeutics in increased doses:
- enteritis, paresis and even paralysis in pigs.
Tranquilizing carbamates (ex. Meprobamate):
- may affect morpho-functionally the hepatic tissue.

Diazepam (benzodiazepine)

produces hepatic disorders, initially weak, which increase in the case of repeated treatments with high doses.

Salicylic acid is dangerous to administrate to:

- cats, species in which determines toxic hepatitis and gastric lesions (e.g.: doses of 30 mg/kgbw, several days = in over 50% of individuals, toxic hepatitis).

Phenacetin and paracetamol, in increased doses and a long period of time: - produce hepatic necrosys (after a serious evolution).

Aminophenazone and phenilbutazone can become:

- hepatotoxic and can cause biliary stasis, cholestatic icterus.

- **Toxic respiratory effects**

Hypnotics, in increased doses, may induce:

- Hypoventilation progressing to apnea.

Changes in the respiratory physiological parameters can trigger:

- bronchitis and bronchopneumonia.
- in newborns respiratory disorders are always serious.

Phenotiazines can:

- Depress the respiratory nervous central system and
- induce tracheo-bronchial paralysis.

Narcotic analgesics:

- depress the respiratory centers from the physiological stimulant (CO_2) and
- Produce bronchial muscle spasm, often followed by exitus.

- **Nephrotoxic effects**

Approximately 40% of the antibiotics (e.g. oligosaccharides and polypeptides) have nephrotoxic effects.

They achieve renal concentration of 10-50 times higher then the usual blood concentration, and thus affect glomerular ultrafiltration and tubular resorption.

More frequent clinical manifestations are:

- albuminuria and
- cylindruria.

-The highest nephrotoxicity from the antibiotics is caused by: kanamycin, neomycin, bacitracin, gentamicin and polymyxin.

Renal disorders caused by sulphonamides are recognized by severe colic consecutive nephron damage (tubular lesions)

Para clinically,

- The nephrotoxic effects produced by sulphonamides can be identified by: haematuria, crystalluria and albuminuria.

Barbiturate derivatives induce:

- Renal failure, resulting dehydration and shock, death through → **respiratory arrest** (in **1-3 days** after administrations).

When evolutions are longer = pulmonary complications.

- In subjects with renal disorders (manifested hormonally) = urinary retention.

Morphine and opium :

decrease diuresis by stimulating the antidiuretic hormone release.

Salicylic acid derivatives determine:

- fluid and electrolyte imbalance + metabolic acidosis (and the appearance of ketones by disrupting the cycle of carboxylic acids) and installation of functional renal failure.

Phenacetin: nephrotoxic effects in long term treatments:

- Interstitial nephritis,

  papillary necrosis,

  pyelonephritis (irritation produced by metabolites in the glomerulus).

Abacterian **nephritis**, **by associating the bacterial factor** → bacterian **nephritis**.

- **Cardio-circulatory toxicity**

Barbiturates can induce:

- tachycardia, hypotension even (in serious forms) tension failure and shock (subsequent to hypoxia).

In general anesthesia, besides hypotension and thrombophlebitis → extension of hypnotic action.

M-colinolytics and alfa-adrenolytics in excess→ tachycardia and finally, hypotension.

Also occurs acute respiratory failure (consecutive to hipoxia due to inhibition of mitochondrial oxido-reductions.

Diphenylmethane tranquilizers in associations with dicumarinic anticoagulants = bleeding, hypotension and tachycardia.

Carbamate tranquilazers can become cardio-vascular toxics:

- Through arterial hypotension.

- Antidotism

The sum of the measures used to annihilate toxins that entered the body, as well as their effects.

Substances used in combating the toxic effects = antidotes.

These can be: a single substance or a mixture, their action is based on the incompatibilities that are established in relation with the toxic substances.

Depending on their specificity to the toxics, antidotes can be:

- general - with wide range of action, used when the substance that caused the intoxication is not known precisely;

- special (specific) - well established for each toxic substance and which are used whenever the nature of poisoning is known.

- **Idiosyncratic adverse reactions**

Idiosyncrasy (idios = own; sincrazis = interference, mixture, blend,)

Coresponds to congenital intolerance, characterized by qualitatively changed responses following the administration of a particular drug.

Variations of intolerance are the expression of biological dissipation

idiosyncrasy was mistakenly compared with drug allergy but, in the case of idiosyncrasy, one does not have to deal with antigen-antibody type of allergic reactions but with ones with some degenerative somatic properties:

In this way is reached a reaction to a drug, even from its first administration and not after a sensitization (allergy).

The symptomes of idiosyncratic intoxication are different from the allergy type ones.

This incompatibility is due to some genetic particularities, most often due to enzyme deficiencies. These may interfere metabolic degradation of the drugs

Example:

Nitrofurantoin → haemolytic anaemia (glucose-6-phosphate deficiency in red blood cells).

Succinylcholine → apnea, animals with "atypical" plasma cholinesterase.

Because of this, the inactivation of curare for eg. is slow, threatening the life of the animal.

The best known example for installation of idiosyncratic effects is in:

youngsters (prematures, newborns) → toxic effects, even fatal, due to ontogenic absence of some enzymes when administering sulfonamides (hepatocellular icterus) and chloramphenicols ("Grau syndrome" in animals and humans→ lethal cardio-circulatory collapse).

- **Drug allergy**

Active substances, even if they are not allergens, may cause allergic reactions.

The reactions will be mediated by humoral antibodies (Ig) which will lead to antigen – antibody reactions.

Actually is an altered response to the drug as a result of prior exposure and involves immunological mechanisms.

Allergic reactions are caused by drugs with protein structure and also by compounds that can couple proteins and which can trigger antigen-antibody type reactions.

Example:

- penicilamic acid can couple with peptides,
- sulphonamides, dextrans may trigger allergic reactions due to the formation of complexes with proteins.

Drugs act like a hapten that couples with the body's own albumin and acts like an antigen.

The process can occur at the surface of:

- erythrocytes,
- platelet and
- granulocytes, in this case, the hapten (by coupling) transforming a component of the membrane into an antigen.

This, in its turn, stimulates the production of antibodies that persist for a long time.

This means that the body retains the ability in the case of a new contact with the hapten to instantly synthesize antibodies.

If the administration of the hapten is continued (reexposure), it will connect back to the cell surface and form the antigen that will react with the antibody (This combination at cell surface → cell lisys).

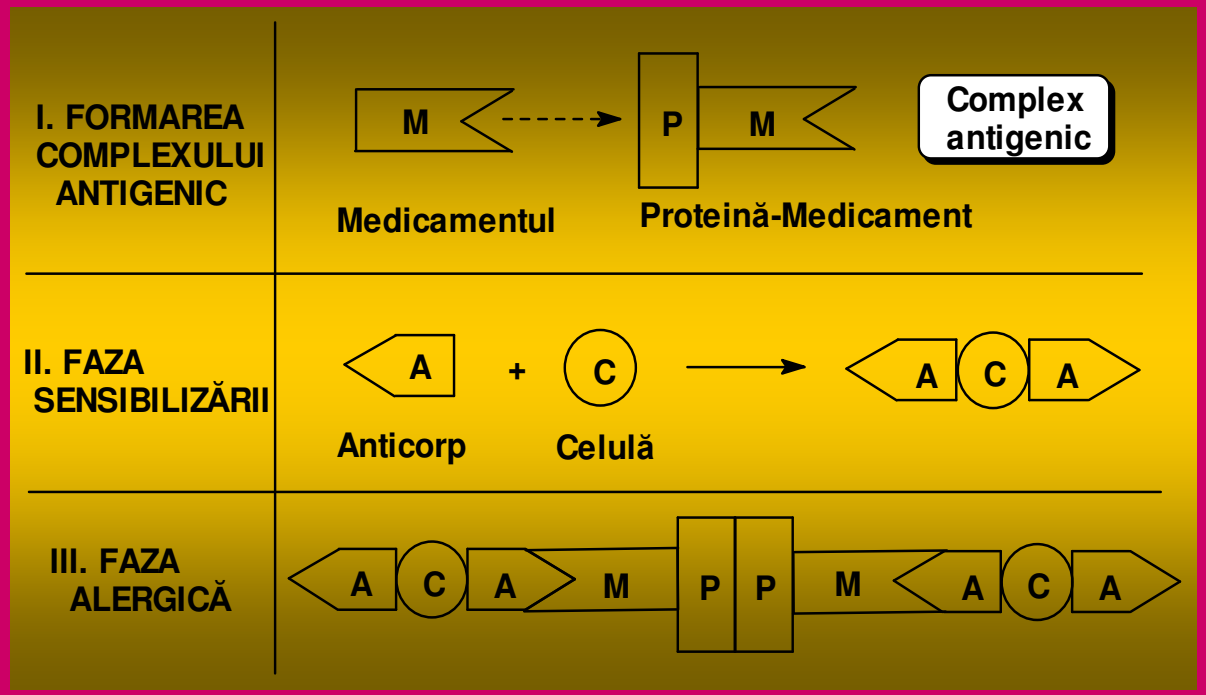
Instead of primary hapten in the reaction can enter also modified active substances or their metabolites, responsible for: allergy to a medication group (ex: sulfonamides, betalactams, benzothiadiazin etc.).

In veterinary medicine drug allergy is installed after topical application, after p.o. administration, rarely post-injection (but much more serious).

reactions = histamine and serotonin release are known after:

- appear only in a part of individuals;
- the response of the body is in the form of severe reactions (even in low doses);
- the recorded reactions are different from the possible usual effects
- there is an initial period, preceding a violent reaction;
-paraclinical may reveal: circulating antibodies in previously sensitized animals;
-patch-tests can demonstrate positive reactions to the tested drugs (ex: scarification test for penicillin highlights anaphylactic hypersensitivity in leisure species).

Simplified mechanism of drug allergy
(after Dragoş 1978, modif. Cristina)



Symptoms associated with allergic reaction may occure:
- immediately or
- after 7-14 days (serum diseases with hyperthermia, arthritis, glomerulonephritis etc., as a result of a disparity between the amounts of antigen and antibody).

Clinically and paraclinically drug allergy is identified by :

- skin rash
- itching and hives,
- asthmatic phenomena,
- haematological changes,
- oedema (Angioneurotic)
- febrile reaction,
- anaphylactic shock,
- dermatitis (delayed allergic reactions)

The majority of allergic sensitization reactions to antibiotics = a consequence of impurities in the manufacture of antibiotics and the specific toxicity of antibiotics and of the compounds in decomposition.

Reactions to antibiotics occur quickly, in 10-30 min after administration.

anaphylactic shock → treated with:

- Antihistamines,
- Cortisone,
- Oxygen and
- Noradrenaline (i.v.).

Certain pharmacons can cause serum disease (ex. alfa-metil-Dopa) (reactions, the immediate and the delayed one, are similar to those caused by allergens: albumin, pollen etc.).

In the subcategory of serum disease :

- skin reactions consequence of photosensitisation or
- of hematopoetic system,
- fever or allergic arthritis.

Medications frequently responsible for allergic reactions in veterinary medicine
(Sinteză Cristina)

Medicamentul	Manifestarea clinică / paraclinică	Mecanismul
Aspirina	Urticarie generalizată, edem angioneurotic	Prin anticorpi IgE
Penicilinele	Şoc anafilactic, anemie hemolitică	Prin anticorpi IgE, IgE/IgG
Digitoxina, Novobiocina, Chinina	Trombocitopenie	IgE / IgG
Aminofenazona, Ampicilina, sulfamidele	Agranulocitoză, exantem morbiliform	Tip celular
Săruri de argint sau aur	Eritrodermie, febrilitate	Tip celular

- **Drug photoallergies**

Photoallergy:

all photosensitivity reactions appearing in a conflict of photo-antigen or photo-alergen – photo-antibody.

After Longhin, formation of photo-allergens is influnced by:

1. substances have different chemical composition and have: animal, vegetal, mineral and pharmaceutical origins.

2. The mechanism of skin photo-sensitisation is: photodynamic and photo-allergic.

Photoreactive substances

Are complex substances that increase skin reactivity to UV or visible radiations (between 2900–7900 Å).

- Generally, molecules that are capable to induce photosensitivity are able to absorb energy from:

  - photons (high)

  - UV-radiation and

  - visible radiation (due to selective absorption of radiation, many of them being colored).
- The majority of substances have a structure of three benzene rings arranged linearly (those ordered in angles have more reduced activity) and MW = 310 -430.
- Many are fluorescent and can form easily free radicals.
- some are:

  - contact allergens (cause contact dermatitis), others

  - are carcinogenic.
- Some (the photodynamic ones) can kill fungal cultures (ex: Candida albicans) by photoxic processes.

Photoallergic reactions have as main features the following:

- **are individual,**
- **occur in animals with lighter hair and skin;**
- **reactions do not occur at the first irradiation, but after successive exposures;**
- **the incubation period is for a few days;**
- **eruptions occur away from the irradiated area, as outbreaks of eczema or urticaria (without residual pigmentation).**

The main substances that are recognized as photo-allergens (Syntesis Cristina)

Substanţe exogene	Externe	Bitionolul, eozina, gudroanele, hexaclorfenul, lavanda, plantele din familia Umbelifere şi Rutacee care conţin furocumarine (angelica, bergamotul, căpşunile, coada şoricelului, frăsinelul, morcovul, muştarul, păstârnacul, mărarul, mohorul, păpădia, pătrunjelul, pintenul cocoşului, portocalul, rapiţa, sunătoarea, teiul, troscotul, ţelina, volbura, etc), rivanolul, tripaflavina, sulfamidele, uleiurile volatile, vanilia.
	Interne	Acridina, albastrul de metilen, antihistaminicele de sinteză (fenergan, romergan), antipirina, argintul, atebrina, aurul, barbituricele, chinina, chinidina, fenocumarinele, fenotiazinicele, griseofulvina, hematoporfirina, neoxazolul, PAS – sodic, sulfacetamida, sulfadiazina, sulfamerazina, sulfametinul, sulfanilamida, sulfapiridina, tetraciclinele,
Substanţe endogene		Rezultă din metabolismul viciat (dintre care cele mai numeroase sunt porfirinele şi derivaţii indolici)

- **Mutagenic, teratogenic type reactions**

Some a.u.v. drugs can cause permanent mutations.

These can interfere with:

- DNA replication or
- chromosomal configurations (teratogenic)

Example:

- alkylating agents → mutagenic effects due to: alteration of the nitrogenous bases or by cracking the chromosomes.
- There are many drugs, that given to pregnant animals: pyrimidone, phenytoin, fenitoin, CBZ, PBZ, ABZ in ruminants may cause fetal malformations especially in the first part of gestation.

These malformations are translated through :

- fetal growth retardation;
- absence of the soft palate,
- hydrocephalus
- minor or serious malformations and even embryonic death;
- extremity malformations (shortening of the bones)
- skeletal abnormalities.

Teratogenic reactions in animals have been described for:

- CNS inhibitors,
- Immunosupressants (antifolics)
- Antivitamins (K),
- Phenothiazines,
- Diazepam and chlordiazepoxide,
- Morphine
- Heroin
- Meperidine,
- Methadone
- Glucocorticoids,
- Antibiotics (streptomycin, tetracycline) etc.
- sulphonamides

- **Carcinogen adverse reactions**

Some substances can promote the proliferation of cancerous process

They can act:

- either at the site of injection
- either in the digestive tract,in the case of p.o. administration,
- either systemically.

Cancer in animals can be caused by:

- alkylating agents,
- organochlorinated products,
- urethane, etc.
- phenacetin (ureters and bladder cancer)
- phenylbutazone (leukemia).

- Tolerance (habituation) adverse reactions

Tolerance (habituation)

A reduced sensibility to some drugs requires the increase of the dose for obtaining the same therapeutic effect, as another individual who received the usual dose.

The change that occurs is of pharmacokinetic nature.

The incriminated drug will not reach the receptors or the targgeted tissues in active concentrations, identifiable by clinical effect

tolerance may be divided in:

- congenital,

  is connected to species (ex: rabbit's insensitivity to atropine (*Atropa belladonna*) due to the capacity of atropine-specific esterases to metabolize the alkaloid);

- acquired
- is the result of repeated administrations which will lead, in time, to minor pharmacodynamic responses.

  Generally, in the case of the second type of drug tolerance, the decreased effect is due to:
- decrease in receptor responsiveness,
- or to the interference of some enzymatic systems.

In animals, this type of adverse reaction can be identified in:

- sympathomimetic amines (e.g., ephedrine),
- cholinergic vasodilators
- hypertensive medication etc.

In this situations tachyphylaxis was installed (tachis = fast, phylaxys = protection) = rapid tolerance.

This type of tolerance is the result of:

- Rapid development of responsiveness by diminishing the effects within minutes - hours after repeated administrations.

The mechanism of tachyphylaxis in veterinary medicine is still under study, fully known being only in experimental cases.

Another type of gained tolerance is :

Mitridatism

has been identified in individuals which were treated for a long period of time with atropine, arsenic derivatives etc.

Changing the route of administration leads to the loss of this capacity.

In human medicine cross-tolerance in known (ex: etilics become less sensitive to narcotics). Probably this phenomenon exists in veterinary medicine too, but there weren't recorded many alerts,yet.

- **Pharmacodependence**

After WHO is:

” Complex medical condition, psychological, sometimes physical, resulting from the interaction between the living organism and a drug substance, characterized by behavioral changes and other reactions that require continuous or periodic administration of the substance, for the purpose of finding the psychological effects and sometimes to avoid the morbid condition resulting from deprivation”.

This condition can often be accompanied by a state of tolerance, same individual may be dependent on several drugs.

Repeated adminstration, with the tendency to overcome the usual doses may cause addiction or eufomania.

This type of adverse reaction does not exist in veterinary medicine, only in animals specially trained to identify drugs (dogs and pigs) or more rarely in horses doped for competition.

It seems that tolerance and dependence (opiates, morphines) is due to retrograde inhibition of the synthesis or release of endorphins.

Tolerance = endorphin deficiency (that will leave a growing number of free receptors that will attach opiates).

when administration is suddenly suppressed = withdrawal syndrome.

In connection with this fact a hypothesys was issued, some individuals are predisposed to opiate habit, precisely due to genetic deficiency in endorphin

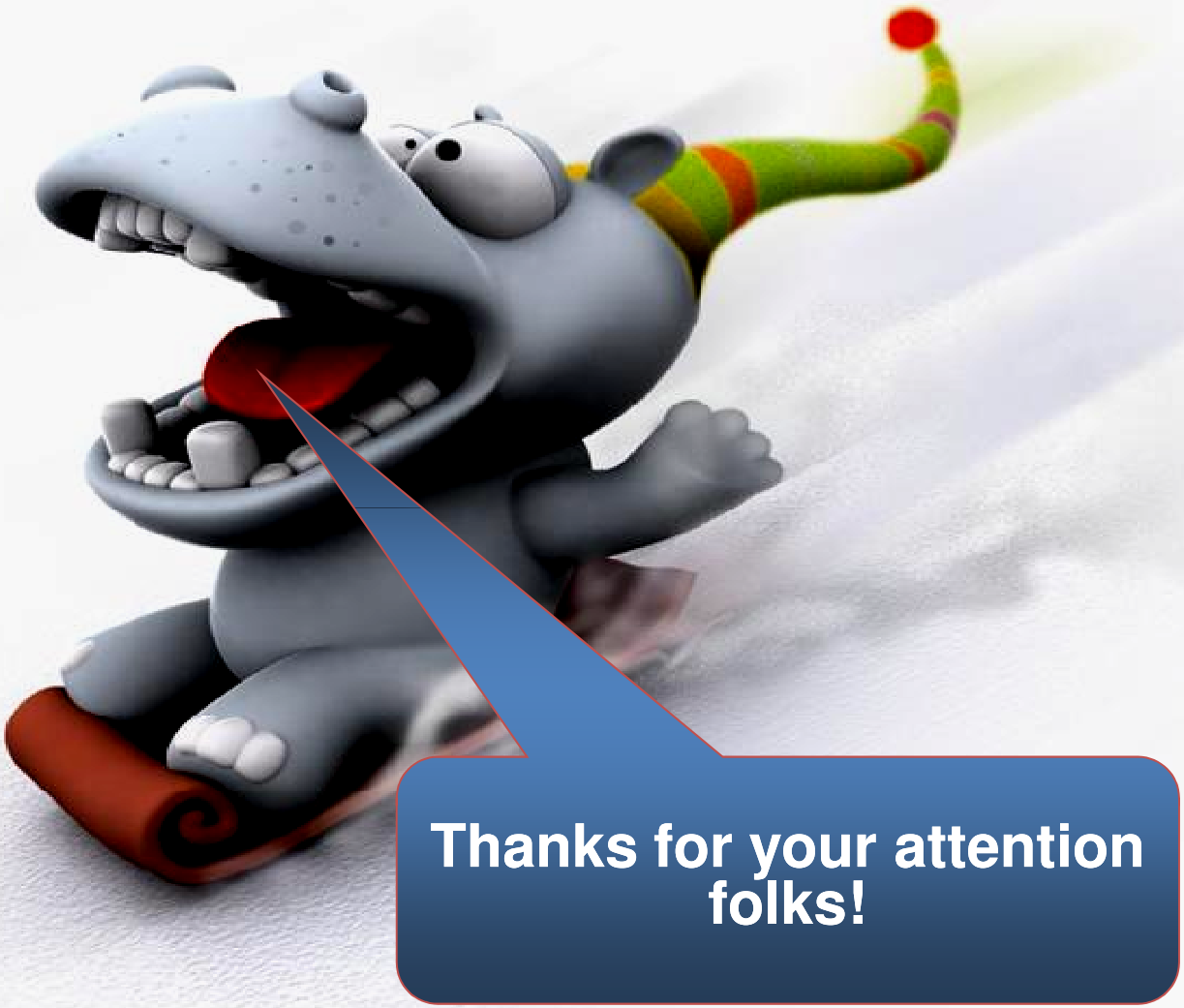
Pharmaco-thesauriosmosis is also considered a side effect

it consists in the accumulation of drugs in tissues for extended periods of time (months - years), which **can exercise or not serious effects** and injuries: haemorrhage, sclerosis, tumours).

In general, in animals the locations are :

- adipose tissue (eg organochlorinated insecticides)
- skin and appendages (eg, arsenic, sulfur, etc.)
- kidney (eg salts, especially of calcium),
- the reticuloendothelial system in the liver and spleen (eg salts of heavy metals, salts of gold, iron, PVP etc.) and less frequently
- central nervous system (e.g., phenytoin).

To alkaloids, habit is installed by enhancing the possibilities of organisms **to inactivate** (usual through oxidation) the substance.



Imagine: www.funnypics.org.uk/ funny-animal-pics.htm