C.2. Administration & Drug absorption

See: www.veterinarypharmacon.com

Prof. Dr. Romeo T. Cristina
The Invasion and evasion scheme
(Cristina RT, 2000)
The administration formulation (dosage)
Is the pharmaceutical preparation in which the active ingredient can be found and which is administered in the body under this form.

In order to obtain therapeutic effects, the drug should come in contact with the body, specifically with the sensitive cells (responsible for the effect) of the body.

This contact can be accomplished using a variety of ways: ways of administration.
The ways of drug administration are chosen depending on the:

- Substance’s physical-chemical properties
- Place of action
- Animal’s condition and
- The speed and intensity with which drugs are expected to act
The period that elapses from:

- the moment the substance is administered

until the substance starts acting = the latent period
The latent period is based on the way of administration and depends on:

- absorption speed,
- transport time in the organic liquid mediums,
- diffusion duration in tissues,
- time needed to produce biological changes that will trigger the therapeutic effect.
The correlation between diffusion into the tissues and the effect installation

A = the absorptions speed
T = the transportation time
B = rate of diffusion
D = the release time lag of the biological modifications

L = A + T + D + B
The ways of drug administration

Has a particular importance for the success of a treatment and should be chosen wisely.

If an urgent pharmacodynamic action is needed, the I.V. way is preferred. But at the same time, it is to be considered, that in this way drugs can come very quickly in contact with the tissues. So, the action can become brutal and potentially dangerous.
Some drugs can be administered only in one way, for example:
- Suzotril can be administered only I.V.,
- Acaprin, only S.C.

Sometimes the drug effect varies depending on the way of administration.
Magnezium sulphate, administered in an:
• enteric way = generates a purgative effect,
while in a
• parenteral = the CNS depressing effect.
Local or topical treatment

is represented by:

• application of powders and ointments on the skin,
• instillation of drops in the eyes and ears,
• injection through mammelons with solutions and / or soft formulations,
• introduction of pessaries in the uterus lumen.
Topical administration

puts the remedy in direct contact with the site of action in the highest possible concentration, reducing the risk of damage to the other organs.

In many cases the absorption of the drug at the administration site, is not desired.

On the contrary, when a generalized or systemic response, is followed, or when the target organ is far from the administration site, the drug absorption is essential.
Absorption

Is the process in which the active substance:

▼

Emerges out from its formulation

▼

And **passes** from the administration site

▼

**into the bloodstream.**
Systemic effect

can be achieved by oral or parenteral administration of the medicinal preparations.

As such, the method of the drug preparation will determine the route of administration.

For example, percutaneous absorption is sufficient to secure the systemic effect of the pour-on (ex: Ivomec pour-on). ectoparasiticides.
Drug formulations

Are prepared by taking into account, biopharmaceutical and pharmacokinetic considerations.

The selection of the remedy of choice is made by the clinician, depending on the intensity and duration of the desired effect.

Each administration route has its own advantages and disadvantages,

The nature and number of different membrane barriers that the drug must cross, largely influences the absorption rate.
Doses

Vary depending on the administration route. Sometimes these variations are very high: for example.

**Strophantines dose in rabbits / kg.bw. is:**

- 0.0003 g, for the i.v. way,
- 0.001 g, for the s.c. way and
- 0.040 g, for the oral way,

This **ratio** of **1:3:133** between these ways of administration is suggestive!
There are: natural and artificial ways of administration

The natural ways

consist of drug administrations to the surfaces of the body that physiologically come in contact with the exterior environment. These are skin and mucosa (divided in):

- apparent (conjunctive, nasal, bucal, vaginal)
- inapparent (bronhic, tracheal, esofagian, gastric, intestinal).

The mucous ways are:

- digestive,
- respiratory,
- genito-urinary,
- galactophore and
- conjunctive.
Artificial ways, are known as parenteral (para = beyond; enteron = intestine).

They involve forming continuity solutions in which active substances will be introduced into the dermis, subcutaneously, in muscles, veins, arteries, serous cavities and other different organs:

- i.d.,
- s.c.,
- i.m.,
- i.v.,
- i.a.,
- intraosseous,
- intraarticular,
- intrasynovial.
Artificial ways started being used with the invention of the syringe by Czech Pravaz (in 1835)

They are meant to put the active substance in direct contact with the tissues inside the body, avoiding the external barriers.

The ways of administration are classified into:

- internal (oral and rectal) and
- external (all other pathways).
Absorption

Has a more important role when the pharmacons are not injected directly into the bloodstream and relies on the physical processes of diffusion and distribution, which are influenced by active biological processes (ex. the transport against the concentration gradient of the potassium, selective transport of the carbohydrates etc.).

The absorption rate depends on:

• way of administration,
• preparation form and
• The drug’s physicochemical properties
The absorption of the drug is considered complete when it reaches the site of action or the bloodstream.

**Main factors** that favor the absorption:

- ✓ molecule size,
- ✓ low polarity,
- ✓ high liposolubility,
- ✓ rich blood irrigation and
- ✓ good permeability at administration site
Oral way is more often used in human medicine, but it is also common in veterinary medicine, where in most cases, a forced administration must be performed.

Oral way is useful for tasteless drugs or with a taste that can be easily masked, especially for mass administration (in forages or in water).

Orally can be administered the:

- biostimulators,
- anthelmintic and coccidiostatic substances,
- antiinfectious ones,
- vitamins,
- minerals, etc.
Oral way - disadvantages:

In the digestive tract, drugs suffer modifications (ex: penicillin G, adrenaline, most hormones- inactivation determined by the gastric acid).

Digestive mucosal modifications like gastroenteritis lead to absorption rate modification, introducing the phenomenon of **malabsorption**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive diffusion</td>
<td>Mouth (M), Stomach (S), Small intestine (Si), Large intestine (Li), Rectum (R)</td>
</tr>
<tr>
<td>Absorption by connection</td>
<td>M, S, Si, Li, R</td>
</tr>
<tr>
<td>Active transport</td>
<td>S, Si, Li</td>
</tr>
<tr>
<td>Passive transport</td>
<td>Si</td>
</tr>
<tr>
<td>Tonic</td>
<td>Si</td>
</tr>
<tr>
<td>Pinocitosis</td>
<td>Si, Li, R</td>
</tr>
</tbody>
</table>
Remedies for oral administration in veterinary medicine include:

- solutions,
- suspensions,
- mixtures,
- pills,
- capsules,
- tablets,
- powders,
- granules,
- boluses and
- premixes.

**Oral mucosa**

Though it is not a mucosa with an absorptive profile, it allows the absorption of **hydrosoluble** substances.
Drug administration into milk in calves

Watering System VAL adaptable to Medicator type system for drug administration

Administration with a dosing piston and simple drencher in sheep
Between the portions of oral mucosa, sublingual mucosa, thin and richly vascularized, absorbs the best.

**Per lingual or sublingual way**

This method is used exclusively in human medicine for a relatively low number of substances (ex: nitroglycerin, trinitrin, isoprenaline, sexual hormones etc).
Drugs that are absorbed in the oral cavity escape to the gastric acid.

**In ruminants**
The contact time of substances with the oral mucosa is longer than with other species.

**Oral cavity**
It is used in order to obtain a local effect in the case of oral cavity diseases or pharynx.
Technique for administration of oral pastes

Boluses administration in sheep
To remember!

The ruminal capacity is considerable and the pH of 5.5-6.5 confers the capacity to function like an ionic trap for drugs with an alkaline character.
fermentative activities and specific microbial populations also influence the chemical stability of certain drugs (chloramphenicol, tetracyclines, sulfonamides and trimethoprim, etc).

• The degree in which orally administered drugs can escape from the regurgitation reflex will determine the pH of the environment in which they are introduced (as long as the abomasal pH value is 3).
Pre-stomach mucosa

has a high absorption capacity.

In the ruminal space:

numerous drugs can be absorbed from the group of:

- vitamins B (thiamine, riboflavin, pantothenic acid, nicotinic acid, cyanocobalamin),
- alkaloids (caffeine, strychnine),
- sulphonamides,
- antipyrine,
- methylene blue,
- alcohol and ammonia,
- minerals (Na, K, Cl, Ca, Mg), etc.
Orally administered drugs can avoid the regurgitation reflex by closing the esophageal tray, therefore end up directly in the omasum or abomasums.

**In the absorption process:**

- **Undissociated component** is the one that
  - penetrates **freely**, according to the concentration gradient.
  - **Dissociated components** will be submitted to the restrictions through electric charges and therefore, they will not absorbed.
Gastric mucosa in monogastrics,

The stomach condition can determine a delayed absorption from the result of feeding,

**For example:**
The pylorus can be closed a time period after feeding, thereby the drugs selectively absorbed in the small intestine, would be delayed from their action.
knowing the dissociation constant of the drug (pKa) and pH for the digestive tract compartment, we can calculate the absorption percentage using the Henderson - Hasselbach equation:

- **weak acid**: \( \text{pKa} = \text{pH} + \log \left( \frac{\text{Cn}}{\text{Ci}} \right) \)
- **weak base**: \( \text{pKb} = \text{pH} + \log \left( \frac{\text{Ci}}{\text{Cn}} \right) \)

Where: 
- \( \text{Cn} \) = deionized concentration
- \( \text{Ci} \) = ionized concentration

For example, sulphadimerazine, having pKa = 7.4 will be present in the rumen (pH = 5.4) **undissociated, almost entirely**, which will allow a good absorption.
In order to be absorbed, a drug needs to be **soluble in fat drops**, as well as in the **aqueous phase** of the intestinal content.

Insoluble compounds will not be absorbed (ex: barium sulfate).

**The gastric mucosa**

- is an **excretion** mucosa and **not** an **absorption** one!

For this reason, absorption on this level will be, in general, **slow and reduced**.

Although, numerous substances are absorbed here (ex: aspirin, alcohol, caffeine, strychnine, PP vitamin).
Plenitude of the stomach
Influences the absorption!

Inside a full stomach, drugs will combined with some organic substances. The absorption will be better when the stomach is empty.

The active substances covered with layers of keratin, gluten, salol, or formalin-gelatin, do not dissolve in the stomach and because of this, these substances are prepared in gastro-resistant tablets and/or pills.
The gastric absorption duration depends on a series of factors:

- **drug type** (liposoluble, hydrosoluble),
- particles size,
- ionization constant,
- pH of the gastric content,
- **physiological conditions** (vascularisation, secretion, tonus, motility) and
- state of stomach plenitude
Liposoluble substances can be absorbed much easier than the hydrosoluble substances (in the ionized formulas they are not absorbed at all).

**Dissociation coefficient of the drug** $^{(pK_a)}$ and the pH of the gastric content are the most important factors of absorption.

At a strong acid Ph of the gastric juice the most absorbed are the weak acids while the basic ones do not absorb.
Therefore, in the stomach: salicylic acid, aspirin and barbiturates will be best absorbed, which at this pH will not dissociate, or only in a very reduced percentage.

**For example:**
If we consider the theoretic distribution of a weak acid drug (having the pKa = 4 value), it can be found that in the stomach (at a pH = 1), 99.9% will be found undissociated and it absorbs and only 0.1% will be ionized, while in the plasma the exact opposite will happen.
Drug absorption can also be **hastened or delayed** through other ways. Therefore, concomitant administration of isotonic solutions at body temperature, hastens absorption through “solvent drag”.

**For example:**
alcohol, saponins, bile salts, are producing the hyperemia of the gastric mucosa and raising the absorption.
Because the gastric pH is usually placed between 1 and 3, and the intestinal pH exceeds the value of 5, it is expected that the absorption rate of the same drug, will vary a lot in both instances.

The difference will depend on the drug's $pK_a$. 

Internal ways
The pH influences the ionization of weak electrolytes.

<table>
<thead>
<tr>
<th>$\text{pK}_a - \text{pH}$</th>
<th>% Undissociated Weak acid</th>
<th>% Undissociated Weak base</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>0,10</td>
<td>99,90</td>
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<tr>
<td>-2</td>
<td>0,99</td>
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<tr>
<td>-1</td>
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<td>90,91</td>
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<tr>
<td>-0,7</td>
<td>16,60</td>
<td>83,40</td>
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<tr>
<td>-0,5</td>
<td>24,00</td>
<td>76,00</td>
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<td>50,00</td>
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<tr>
<td>+2</td>
<td>99,01</td>
<td>0,99</td>
</tr>
<tr>
<td>+3</td>
<td>99,90</td>
<td>+0,10</td>
</tr>
</tbody>
</table>
Esophageal mucosa

It does not matter for absorption!
In special cases (e.g. esophageal diverticulum in birds or esophageal obstructions in mammals), absorption can occur due to prolonged stagnation of drugs in this segment.

Intestinal mucosa

- regarding the drug absorption capacity, the intestine behaves like a lipoid membrane with pores and transport systems.
Intestinal absorption
Can occur in the entire length of the intestine, regardless of the histologic differences or pH between the different segments of the intestine.

In case of oral drug administration, the rich vascularization and the large absorption surface of the small intestine makes it the most important absorption place.
The intestinal mucosa and absorption

The large surface, the presence of numerous villi and the rich vascularization (presence of a massive lymphatic and blood vessel network) ensures a high absorption capacity. Absorption mechanisms through intestinal mucosa are grouped into two categories:

- unsaturable passage (passive transport);
- saturable passage (active transport).

The majority of drugs are absorbed through passive diffusion in the gradient sense of concentration (based on Fick’s law).
The correlation between pH of the intestinal medium and the drug pKa is important in absorption, due to the Henderson-Hasselbach equation.

In the intestine especially the weak bases (with pKa lower than 8) are absorbed, and in some extent, organic acids with pKa lower than 3.
The absorption through the intestinal mucosa is selective!

Thereby,

from the inorganic substances, monovalent ions are much easier absorbed, while the bivalent ions will be absorbed with much more difficulty.

The **organic substances** are better absorbed in a **liposoluble undissociated form** than as a dissociated form.
When the intestinal mucosa is damaged the absorption will be unselective!

In the case of hemorrhagic gastroenteritis, the substances that normally are not absorbed, or only in a low percentage (acting locally), can pass into the bloodstream causing poisonings (ex: nitrofuranul, furazolidone, anthelmintic etc.).

The factors that influence the bloodstream and the intestinal mobility can rush or delay the absorption.

The substances that produce intestinal vasoconstriction decrease the absorption, while vasodilatation correlates with a faster absorption.
The intestinal absorption also influences the mode of action of drugs.

Thereby, the orally administered streptomycin in the digestive tract will act locally, with an absorption rate of only 5% (in dogs, up to 10%) and that’s why it cannot be used in generalized infections.

The substances that are absorbed in the stomach and intestine get into the portal circulation where they will meet the hepatic barrier.
Here:
• a part of the drug will be metabolized and then eliminated and
• a part enters into the bloodstream, another being eliminated through bile, getting back into the intestine, forming the **gastro-entero-hepatic circuit**.

For example tetracycline enters into the **enterohepatic circuit** and can accumulate into the body by overdosing.
The large intestine absorption

Through the mucosa of the large intestine, substances with low molecular weight and residues of drugs that have not been absorbed in the small intestine, can be absorbed

The rectal mucosa is used for absorption, being considered an internal administration way. The substances that are administered in a rectal way (enemas and suppositories) are absorbed and enter into the posterior hemorrhoidal veins, arriving into the vena cava, traversing hepatic barrier.
Because of that, the consequence will be a **faster diffusion** into the body and a **metabolisation delay**.

In veterinary medicine, rectal administrations are used as **enemas or suppositories**, usually in pets.

For example, **chloralhidrate**, is administered generally as narcotic enemas in horses, or also as an antidote in strychnine poisoning in dogs.
Research showed that, after rectal administration the blood concentration is not predictable and most of the times it is much less then required.

When a substance is decomposed quickly in the liver, a significant difference can appear between the determined effects in the case this substance was administrated sublingually or enteric.
As a conclusion, the absorption at the intestinal level is dependent to the following main factors:

- **Physicochemical properties of molecules:**
  - the size,
  - solubility,
  - dissociation degree of acids or bases,
  - the characteristics for a specific physiological transport mechanism etc.

- **The form and availability of Galenic preparation** (solution, powders, tablets, pills) and features like:
  - particle size,
  - the rate of decomposition
  - drug consistency (mass of incorporation)
Administration on the external ways
Inhalation way

It is an important way of administration for some specific drugs, especially for the ones from the sphere of anesthesiology.

Using this way active substances under a gaseous form, liquid, or even very fine solid particles, are administered to animals.

The absorption can be produced at a respiratory level, or in the pulmonary alveoli.

The respiratory mucosa has the advantage of a large area of absorption, with rich vascularization and in direct contact with the alveolar epithelium of the capillaries.
This way, gaseous substances like: oxygen, carbon dioxide or the mixture of CO$_2^{(5\%)}$ si O$_2^{(95\%)}$, known as carbogene, are administered.

The carbon dioxide is the physiological stimulator of the respiratory center!

Inhaled in the concentration of 5\% of the atmospheric air, will amplify the respiratory movements.
Volatile drugs are administered largely by the respiratory route.

Currently, in narcosis, a series of substances are used, like: chloroform, ether, ethyl chloride, halothane etc.

Numerous volatile oils (ex. eucalyptol gomenol, are applied locally under the form of drops in the nasal mucosa or they are administered under the inhalation or fumigation formulas.
Inhalations
Are formulations in which volatile substances are activated by water vapors and then inhaled by the respiratory system.

Fumigations
Suggest the burning of antiseptic substances and the inhalation of the produced smoke.

Aerosols
Are small liquid or solid particles suspended in air, administered by the respiratory way.
Profundity of penetration of aerosols inside the respiratory system depends on the particle size.

**Thereby, particles:**
- over 30 μm remain into the nasal cavity, pharynx and larynx
- between 20-30μm remain into the trachea,
- 10-20μm into the bronchi,
- 3-5μm into the bronchioles,
- under 3μ enter into pulmonary alveoli.

The optimal penetration size for the pulmonary alveoli are of: 1 -3μm.

Bigger particles cannot enter, and the ones under 1μm will be eliminated through exhalation.
Intratracheal injections,
Are considered to use the respiratory route of administration.

The substance is deposited on the respiratory mucosa and after placing the animal in lateral decubitus on an inclined plane, it is allowed to escape through the gradient in the lung. This is the way the Lügol solution is administered in sheep dictiocation, rarely in calves, (iodine 1,0; potassium iodine 1,5; distillate water ad. 1500,0) the first administration it is made in one lung and the second is made after 24 hours in the opposite lung.
Inhalation systems.
- for big animals (Nebul 101)
- for average animals (Nebul 81)

Intratracheal administration.
- puncture and the catheter introduction;
- the catheter route into the trachea.

Oral spray with two or three phases
Absorption through the apparent mucosa
Drugs that are administered on the apparent mucosa will have a differential absorption.

**Conjunctive mucosa**
It is easily permeable for drugs.
It is used for local applications, especially antiseptics, chemotherapeutics, antibiotics, anesthetics, miotics and mydriatics.

The administrations are made under the form of eye washes.

The solutions should be neutral and isotonic.
Nasal mucosa
It is used for local applications or for inhalations of the volatile oils through the airways.

Generally, the nasal mucosa absorbs drugs well and for this reason, it can be used with efficacy in small animals for general treatments.
**Vaginal mucosa**

It is a less permeable layer to drugs, but can be traversed by liposoluble substances.

**Uterine mucosa**

Especially in the puerperium, it absorbs well chemotherapeutics, antibiotics or other substances that need to be locally applied.

**The mammary mucosa**

Is used regularly for the treatment of mastitis. Antiinfective drugs introduced into the galactophore sinus will have a local action.
Absorption through skin
Besides the superficial effect, absorption may occur after the application of certain drugs on the skin, although the secretion of the sebaceous and keratinized epithelium will limit the penetration of liposoluble substances.
The Penetration
of the drugs through the dermis is valued by the formulas that contain fats or organic solvents and by the presence of hair follicles and sebaceous secretion.

The local administration
is characterized by high concentrations of the the pharmacon and can determine the therapeutic effect, but only at the application site, while the amount of the pharmacon that is absorbed into the body is very low.
Drugs can hardly penetrate through skin, being forced to cross a double barrier that consist of:

- a hydrolipidic barrier and
- an electrolyte barrier,
- between which there is a protein gel.

The crossing is done differently depending on:

- The physicochemical properties of the substances and the solvent in which they are incorporated,
- thickness of the skin and
- richness in hair follicles.
The main mechanism of passage is passive diffusion, but also supplemented by the active transport and the pinocytosis.

Passive diffusion of drugs can be achieved in two main ways:

- trans-epidermal and
- trans-follicular route.
The classification of excipients according to the factor of acanthosis  
(After: Cristina RT, 1996)

<table>
<thead>
<tr>
<th>NON-ACANTHOGEN</th>
<th>MEDIUM ACANTHOGEN</th>
<th>STRONGLY ACANTHOGEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>silicone oil, cetaceea, sesame oil, methylcellulose, stearyl alcohol, cetyl alcohol, paraffin, glycerin, propylene glycol, stearin, lanolin hydrate (50%), wax, PEG 400, 1500, 4000</td>
<td>vaseline, animal fats</td>
<td>eucerin anhydrous and hydrated, yellow Vaseline, axungia, olive oil, paraffin oil, sorbitol (70%) Undecilenat acid, cocoa butter 70%</td>
</tr>
</tbody>
</table>
Classification of the pharmaceutical forms by the: penetration degree, action of the vehicle and stage of disease
(After: Cristina RT, 1996)
Transepidermic (transcellular) way is important because of its great surface. It involves the:
- crossing of the lipid film on the surface and
- penetration through, or between of the stratum corneum of the epidermis.

Unionized substances with a balanced partition coefficient (around 1), with small molecules, cross the trans-epidermic layer more easily.
Transfollicular route (intercellular)

is accomplished through the epithelium of the:
- hair follicle,
- sebaceous glands and
- sweat gland ducts.

Penetration by this route is considered easy but the absorption area is much smaller compared to the trans-epidermal way.

The crossing is often made by passive diffusion.
Rubbing or massaging the skin will amplify the percutaneous absorption by removing the stratum corneum and by activating the local circulation.

Ointments using excipients with high penetrating power, will be highly absorbed acting into the depth.

- Dimethyl sulfoxide (DMSO),
- Dimethylformamide (DMFA) and
- Dimetillactamide (DMLA),

Are helping the penetration by the emollient effect and increasing the stratum corneum hydration with destruction and dissolution of the lipoproteins. These substances facilitate the absorption of some drugs (chemotherapeutics, antibiotics), with whom they are associated.
Scheme for the proper use in the external treatment of preparations composed of two-or three-phase systems

(After: Cristina, R.T. 1996)
The parenteral ways
Parenteral drug products are reabsorbed non selectively being stored directly into the tissues or into the bloodstream.

**Parenteral administration**
If by oral administrations, inappropriate systemic concentrations are reached (probably due to incomplete absorption or to the degradation into the intestine), parenteral administration will be required.
The preparations intended for injection should be:

• non-pyrogenic,
• sterile,
• adjusted to the osmolarity and
• to the body’s pH.
The pH value of a solution gives an indication of acidity or alkalinity.

<table>
<thead>
<tr>
<th>The pH value</th>
<th>The solutions reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>under 2</td>
<td>Strongly acid</td>
</tr>
<tr>
<td>2 – 4</td>
<td>Acid</td>
</tr>
<tr>
<td>4 – 6,5</td>
<td>Weakly acid</td>
</tr>
<tr>
<td>6,5 - 7,5</td>
<td>Neutral</td>
</tr>
<tr>
<td>7,5 – 10</td>
<td>Slightly alkaline</td>
</tr>
<tr>
<td>10 – 12</td>
<td>Alkaline</td>
</tr>
<tr>
<td>over 12</td>
<td>Strongly alkaline</td>
</tr>
</tbody>
</table>
The installation of an effect can be:
- delayed, by s.c. administration,
- Rapid, by i.m. administration and
- Immediate, by i.v. administration

The parenteral administration avoids the disadvantages of the oral administration, but requires a sterile injection technique.

The parenteral ways eliminate the need of a drug to cross a mucosa, as a first step in the process of absorption.
The evolution of the effective concentration depending on the chemical nature of the active principle.

**The serum concentration**

- **sare de sodiu**
- **sare de procaină**

**The time (h)**

**Route and site of administration**
- i.m.-the buttocks muscles
- i.m.-croup (the gluteal fossa)
- s.c.-croup
- s.c.-lateral side from the back of the shoulder

**Plasmatic peak**
- 3,9
- 4,6
- 3,3
- 4,6
Intradermal way (i.d.)

▲ Intradermal injections are generally used for:
- diagnostic purposes (such as bovine tuberculin),
- for testing drug sensitivity to certain substances or,
- in case of allergenic tests.
Subcutaneous way (s.c.)

There are selected places with accessible rich connective tissues, less traversed by large blood vessels and nerves.

This way is chosen when a slow but continuous absorption of the drug is necessary, although often the absorption rate is the same with intramuscular administration. (phenylbutazone and chlordiazepoxide).
The drugs are absorbed through the capillary network and the effect appears generally after **10-15 minutes**.

Resorption is amplified by hyaluronidase, that can be added to the injection solution. This will depolarize the hyaluronic acid, found in the intercellular substance.

**Resorption rate** can be increased by heat and by massaging the injection site.

These measures can be applied when administering large **volumes of saline**.
<table>
<thead>
<tr>
<th>Nr</th>
<th>The length</th>
<th>Indications</th>
<th>The code</th>
</tr>
</thead>
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<td>yellow</td>
</tr>
<tr>
<td>2</td>
<td>0,80 x 40</td>
<td>i.m., i.v., venesection</td>
<td>green</td>
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<tr>
<td>12</td>
<td>0,70 x 30</td>
<td>i.m., i.v.</td>
<td>black</td>
</tr>
<tr>
<td>14</td>
<td>0,60 x 30</td>
<td>i.m., i.v. in small animals</td>
<td>blue</td>
</tr>
<tr>
<td>16</td>
<td>0,60 x 25</td>
<td>i.m., i.v. in small animals</td>
<td>transparent</td>
</tr>
<tr>
<td>17</td>
<td>0,55 x 25</td>
<td>i.v., s.c. in small animals and birds</td>
<td>violet</td>
</tr>
<tr>
<td>18</td>
<td>0,45 x 23</td>
<td>i.v., s.c. in small animals and birds</td>
<td>brown</td>
</tr>
<tr>
<td>20</td>
<td>0,40 x 19</td>
<td>i.m. in small animals and birds</td>
<td>white</td>
</tr>
</tbody>
</table>
Regarding the absorption mechanism, this is different for oils and aqueous solutions.

The oily solutions reach the lymphatic vessels by:

- penetrating the endothelial cells, or
- passing on (firstly the substance, after the oil)
Isotonic substances are absorbed faster than the isotonic solutions, and they are more easily absorbed than the hypertonic solutions.

The drugs are typically soluble in saline or distilled water, rarely into the polyvinylpyrrolidone (PVP).

Subcutaneously, organic and tissue implants may also be administered by the form of hormonal micro tablets with a slow absorption rate.
Intramuscular way (i.m.)

The veterinarian chooses the intramuscular route when:

- he administers relatively irritating substances;
- when the absorption rate of the drug administered subcutaneously is unsatisfactory
For the administration of the deposit type preparations (ex: iron-dextrane in piglets with iron deficiency anemia);

When the injection substance is not a solution but it is for example, a suspension.

The diffusion of solutions occurs over a wide area and the osmotic balancing in the case of slightly hypertonic solutions is fast.

Parenteral pathways
The fact that the sensory innervation is reduced, makes the local tolerance to be higher.

The solutions with a high acid or basic pH, those highly hypertonic and the caustic ones cannot be administered, because they can produce: indurations, phlegmons, abscess or necrosis.

Besides, in animals, unlike humans, the intramuscular way is much more painful.
The intramuscular way can be used for administration of the medical substances into aqueous solutions, oily solutions and fine suspensions.

It is the best way of administering **oily solutions** and deposit medication. (ex: Procaine penicillin, benzathine penicillin, hormones, etc.).

The injections are made **profoundly intramuscular**, this way being less painful and avoiding the risk of the substances entering the blood vessels, which always leads to serious consequences.
The intramuscular administration can be made to every species, into:

- the gluteus muscle or
- the superiors thigh muscles;

The administration can be made also into the superior cervical muscles in pigs, cows and horses.

The volume of liquid injected in a single place should not exceed **10-20 ml**.
The intravenous way

It is the fastest way to introduce drugs into the general circulation, because it eliminates the need for the active substance to cross the endothelial barrier, therefore the total amount administered is immediately available.

The intravenous way is used for:

- plasma or blood transfusion
- when a rapid effect is needed
- when a drug is too irritating to be administered in another way
• for an accurate control of the dose
• for a longer-term administration, using an intravenous cannula for drugs with a transient action

The specific conditions:

That a solution needs to satisfy in order to be administered using the i.v way, except the usual ones (sterile, non-pyrogenic) are:

► should not be hemolytic, coagulant or precipitant,
► should not be toxic for the myocardium,
► should not harm the vascular endothelium,
► should not cause embolia and
► to be close to the body temperature.
In veterinary medicine, as an exception, the i.v. injection of the oiled camphor is allowed, in colic therapy in horses, but in low-doses (3-5 ml) administered slowly.

The i.v. way allows the administration of the substances that are not tolerated by the tissues:
- irritant
- hypertonic, or
- alkaline solutions
Macromolecular substances can be introduced intravenously:

- gelatins (Marisang) or
- dextrans (Vetoplasm)
- colloidal plasma substitutes etc.

The injection is usually made in the jugular vein in:

- horses, cow, sheep and goats.
- in pigs: in auricular veins
- in cats and dogs: in the cephalic vein and the recurrent tarsal veins.
The animals:

- At birth = 75% water
- The fetus = 86%
- The embryo = 95% of its body weight

Throughout the development and maturation, skeletal and body fat development, the water from the body decreases.

Inside the tissues the distribution is different:

- Nervous tissues = 90%
- Epithelial = 70%
- Muscles = 75%
- Bones = 25%
- Fat tissue = 10%

Depending on the species: Equines 67%, Cattle 64%, Donkeys 62%, Ovins 61%, Goats 59%, Swines 50%.

The estimation of the quantity of water from the body can be made using two methods:
The method of heavy water (D2O) and of the tritiated water (HTO).
The water renewal rate represents a "turn over", and in mammals the complete water renewal is made in **20 days**. In **24 hours** the “turn over” varies depending on the species:

- 143ml / kgbw in cows
- 150ml / kgbw in sheep,
- 73ml / kgbw in goats,
- 75ml / kgbw in donkey.

Depending on the intended therapeutic purpose, the infusions can be:
- with electrolytes;
- for the acid-base equilibrium;
- with energy substances
- reconstructing substances;
- substitute solution for colloidal plasma;
- of drugs.
Intraarterial way (i.a.) - rarely used. Disadvantage: achieves high drug concentrations in some peripheral areas.

The intraperitoneal way (i.p.) commonly used, especially in dogs, cats, pigs and large animal younglings, but may be useful in other animals as well. Due to surface and the high absorption rate of the peritoneum, this route is advantageous for the administration of large volumes of liquid.

The injections: into the lumbar fossa (needs to be made carefully in order to avoid injecting the preparation into an abdominal organ).
Intrathoracic and intracardiac injections
Are made occasionally in small animal euthanasia

Intrathecal injections (subarachnoid)
Involves the penetration of the CNS lining.

Epidural injections
In cattle, in case of birth, when the abolition of the uterine contractions is desired. The local anesthetic is introduced into the space between the first two coccidian vertebrae.

Intraarticular injections
Used when administering antiinflammatory drugs and antibiotics into the intraarticular space (especially in horses).

Rectal, vaginal and intramamar injections
Used only when the therapy is needed in this region.
<table>
<thead>
<tr>
<th>injectable preparation</th>
<th>Infusion preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Containing drug substances with a pharmacodynamic activity</td>
<td>Rarely serves as a mode of a drug administration</td>
</tr>
<tr>
<td>May have as carrier besides water: oil and various organic solvents.</td>
<td>The exclusive carrier will be the water.</td>
</tr>
<tr>
<td>The active substances may be dispersed in the form of suspensions.</td>
<td>The active substances are dispersed molecular, colloidal, and rarely emulsions.</td>
</tr>
<tr>
<td>Administrations are made in small or medium units (usually 1-20 ml).</td>
<td>They are prepared and administered in large amounts (usually up to 100 ml).</td>
</tr>
<tr>
<td>They can be administered using the i.m., s.c., i.v., i.d., i.p. way.</td>
<td>The administration is made strictly on the i.v way.</td>
</tr>
<tr>
<td>The duration of the administration is short (seconds, minutes), so it is more comfortable in animals.</td>
<td>The duration of the administration is large (tens of minutes, even hours), are difficult to animals.</td>
</tr>
<tr>
<td>The isotonic and the isohydric are not always required.</td>
<td>The isotonic is required, the pH of 7.4 and the ionic composition, needs to be as close as possible to the body fluids.</td>
</tr>
<tr>
<td>The preparation is made into ampoules, rarely into vials with a low volume.</td>
<td>The preparation is made using vials or packaging with 200-1000 ml without preservatives. For peritoneal dialysis the packaging can be barrels with a capacity of 10-20 liters.</td>
</tr>
<tr>
<td>Theoretic the condition of the pyrogenic (especially for the small amounts of the injected solutions) is less important.</td>
<td>Preparation conditions should provide solutions perfect sterile, without pyrogenic substances.</td>
</tr>
</tbody>
</table>

The differences between injections and infusions
(Synthesis by: Cristina RT, 1999)
Thank you for the attention!