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Drug excretion

See: www.veterinarypharmacon.com

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By drug elimination (excretion) we mean all processes that lead to drug inactivation and their removal through:

- kidney,
- bile digestive tract,
- respiratory tract,
- skin and mucous membranes,
- mammary gland and placenta,

As well as the chemical transformations of the molecule

The measuring unit for the rate of elimination is: the biologic half-life (elimination half-life).

This represents the elapsed period until the amount of the substance in the body drops to half of the initial amount and is a temporal measure that underlies the mathematical transposition of the elimination process.

Plasma half-life time $t_{1/2}$ represents the velocity constant of an exponential process.

To express the removal rate via the kidneys, veterinary medicine has adopted the term: renal clearance.

This is expressed in volume of plasma(ml) occupied by the drug substance excreted over an established period of time(1min.) through the kidneys.

Clearance formula will be:

$$Cl = VuE \times \frac{Cu}{Cp},$$

Where:

Cl = clearance expressed in ml;

VuE = excreted urine volume / minute (ml);

Cu = concentration (mg%) of the drug substance in urine;

Cp = concentration (mg%) of drug substance in plasma .



Of course, the expression of clearance can be used by extrapolation, for the: liver, lung etc.

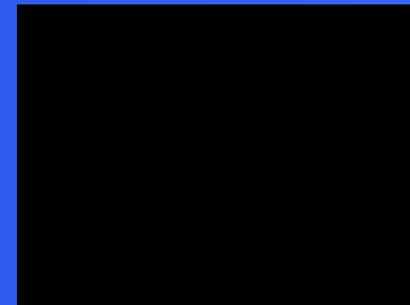
The half-life of a drug in the body can be influenced by:

- ▶ serum proteins capable of binding drugs in the form of complexes,
- ▶ the possibility of tissue storage or
- ▶ metabolism rate.

Kidney and bile (through the liver) are the main organs for drug excretion, and

- saliva,
- sweat,
- mammary gland and
- the lung

are secondary pathways of excretion.



Farmacons may be removed by:

urine and feces, where the highest amount of the administered substance or byproducts resulted after metabolism, can be found.

Liposoluble substances are difficult to be expelled by the kidney (due to the tubular passage which leads to permanent reabsorption).

If there is a strong binding to serum albumin, glomerular filtration rate **remains at a low level**.

Most of the amount of the substance that was filtered suffers a diffusion process in reverse at a tubular level, due to the hydrophobic characteristics of molecules.

Renal elimination rate:

is increased when renal function is impaired.

Substances that are easily removed through the urinary system, can cause elevated blood levels in the case of renal insufficiency.

Substances that have **decreased renal clearance** are indicated in such conditions.

In the feces:

will appear substances that

- are eliminated via biliary route or
- are secreted by the intestinal mucosa.

Elimination by:

- ▶ **sweat, saliva and milk =**
less important quantitatively.
- ▶ **respiration =**
major route of elimination for narcotics.

Some active substances can concentrate at the elimination site and reach local toxic concentrations, eg. renal disorders caused by the compounds based on: mercury, phenols and by aminoglycoside antibiotics.

So:

The route of elimination changes, depending on the properties of the drugs:

- those insoluble p.o. will be eliminated through the digestive tract,
- those soluble are excreted by the kidneys,
- and the volatile or gaseous substances by the lungs.

Most substances that reach the general circulation are eliminated after previously undergoing the processes of metabolism.

2. The form under which drugs will be eliminated depends on what transformations they will go through in the body.

Penicillin, most part (80%) is eliminated by kidney:

- 20% - glomerular filtration and
- 80% - tubular excretion,

almost fully recovering its active form.

Streptomycin and oxytetracycline can be, also, largely recovered in the urine in their active form.

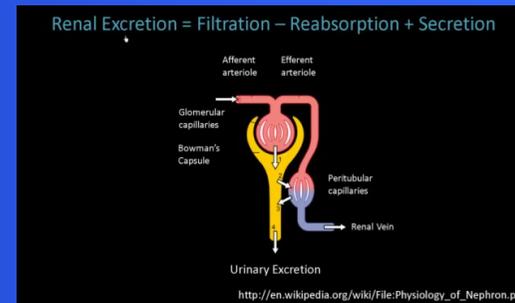
In other cases :

Substances that are excreted unchanged, **produce kidney damage** (eg: cantharides).

The same thing appears in the action of some metabolites.

Acetylsulphonamide precipitates in the acid medium of urine under the form of sharp microcrystals which will damage the renal tubules or will agglomerate in their lumen.

3. A substance administered by the respiratory route (volatile or gaseous) will be **rapidly** absorbed and eliminated.
4. An orally administered substance, which passes into the general circulation and binds massively to plasma proteins (ex: retard sulphamides) or to tissular ones (ex. digitoxin) will be eliminated **slowly**, being maintained in the body for several days.



5. The drug elimination rate depends on:

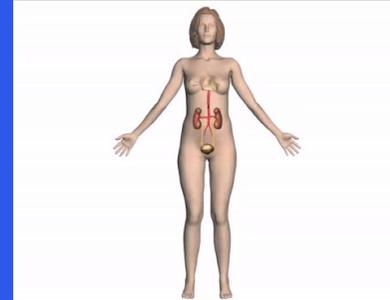
- the route of administration,
- physico-chemical properties,
- fixation to plasma proteins or tissue,
- transformations suffered in body,
- elimination pathway.

When a drug (with renal elimination) is not metabolized, its half life may reach **20-30 days**.

A drug that has a good distribution, in all body compartments and is secreted by the renal tubules, will have (generally) a half-life of **60 minutes**.

In drug elimination various situations can emerge, like:

1. the removal of all the administered substances is **complete** (when we speak of a real elimination), or when,
2. due to various causes, elimination is incomplete and that is usually **apparent**.



Renal elimination

The kidneys are the most important route of elimination, most drugs are partially or totally eliminated here.

The physiological kidney purge takes place in three ways:

- a) glomerular filtration;
- b) tubular excretion;
- c) glomerular filtration and tubular excretion

During circulation, plasma = filtered by the glomerule.
glomerular membrane, (as the capillary wall)



▼▶▶▶ allows the passage of small molecule
solutions and substances.

The filtrate passes ▶▶ in the renal tubules (lined with
interlinked epithelial cells, forming a continuous
membrane with lipoid features).

During its passage through the tubes and the collecting tubules, **99%** of the filtered water is **reabsorbed and the urine will be concentrated.**

At the same time, **non ionized** liposoluble substances may be **reabsorbed**, creating an equilibrium between plasma and renal tubules.

Organic molecules pass through the tubular membrane, respecting the same conditions that apply to other membranes of the body (according to the concentration gradient).

They depend on the :

- **Physico-chemical properties** of the substances (molecule size, partition coefficient, pK) and
- **pH** of the urinifery tubes.

Only **non-ionized** drugs may be reabsorbed in the tubular epithelium (ionized form of the majority of weak acids and bases is liposoluble)

As such, the amount of drug excreted will be in accordance with the pH of the content of the tubules (Henderson- Hasselbach).

Organic molecules are weak electrolytes and at the urinary pH are **partially ionized** and partially **unionized**.

In general, **the excretion** of drugs with a pKa of:

- ▶ 3,0 - 7,5 for weak acids and
- ▶ 7,5 - 10,5 for weak bases

is **pH dependent** and deeply affected by urinary pH.

Alkaline drug excretion

- is increased: by acidification of urine and
- is decreased: through its alkalization (and vice versa).

Thereby,

Procaine (weak base) with $pK = 8,95$ is eliminated 10 times more in acid urine.

Amphetamine is less eliminated (5%) when the urine $pH = 8$ (at this pH is almost entirely unionized and is reabsorbed) and over 50% in urine with a $pH = 5$

Aspirin (weak acid) with $pK_a = 3$ is eliminated 80 times more in alkaline urine than in acid urine.

Changing the urinary pH by acidification or alkalization, will lead to the **alteration of the elimination process.**

Tubular excretion

is performed by specialized transport in the epithelium of the proximal tubule and is the most important route of elimination.

There are two specialized transport mechanisms:

- a.** One which transports ionized forms of acid drugs (ex. salicylic acid, penicillin, probenecid, sulfa acetylated, glucuronides and ester sulfates, etc.) and
- b.** one which transports ionized forms of basic drugs (for histamine, thiamine, hexamethonium and other quaternary ammonium derivatives etc.).

These two mechanisms have the characteristics of the active transport :

- **against the concentration gradient** (dependent on the energy supply).
- **there is a competition** between weak acids and weak bases.

Renal elimination can be accelerated by :

- **increasing diuresis,**
- **urinary pH change**
- **preventing tubular reabsorption.**

Drugs metabolized by the body are more easily removed, because they are transformed in water-soluble compounds.

The function status of the kidneys influences the rate of elimination.

In case of kidney failure, the removal process takes much longer.

Thus, **streptomycin** is eliminated normally **60-80%** during the **first 24 h**, by glomerular filtration.

In case of renal failure, elimination decreases to a rate of **2% in 24 h**.

Fulness of the digestive tract may influence the half life of a drug.

A water-soluble drug administered prior to feeding can be eliminated renaly **after 10 min.**

The maximum removal will be **at 60 min.**, it then decreases gradually (due to glomerular filtration and partial reabsorption).

Elimination through the digestive tract

Many insoluble or poorly soluble drugs administered orally, have a local action in the digestive tract, where they achieve significant concentrations and are eliminated in the faeces.

Through the digestive tract, a number of substances are eliminated, that diffuse passively more often than not, from plasma through mucous membranes or glands of the digestive tract.

In the saliva, a number of drugs can be eliminated. Such as bromine, iodine, Hg, Bi and Pb salts.

Through the gastric mucosa and gastric juice, a number of drugs such as: **alkaloids and halogenated derivatives** are also eliminated.

The factors that increase elimination through the gastric mucosa are:

- those who activate the local circulation and
- those who increase the gastric secretion.

The mucosa of:

The **forestomach, glandular stomach** and **intestine**, behave as semipermeable membranes for drugs in blood plasma.

They are crossed in both directions by the free fraction, depending on the concentration gradient.

The amount of drug that, after oral administration, can be found in the faeces, is composed of :

- **unabsorbed drug and**
- **the product recovered in the intestine.**

Drugs access the digestive tract through:

- **the intestinal wall,**
- **its secretions**
- **bile,**

by diffusion or by active transport.

Biliary excretion

Low molecular weight drugs (under 150kD) are excreted by the kidneys.

Biliary excretion of **large molecules**, indicate that the membrane of the bile and the hepatic sinusoidal blood, is highly porous and allows the penetration of molecules and ions weighting less than plasma proteins.

The vast majority of the drug excreted in bile, is found in **conjugated form**.

Glucuronide conjugates are excreted in bile.

Pancreatic juice

- may bring, in the case of oral administration, by passing inside the duodenum, tinctures or chemotherapy.

Hepatic cell

- is permeable for liposoluble drugs and
- has limited permeability for polar drugs,
- eg. antibiotics that achieve high proportions in biliary secretion:
tetracycline, chloramphenicol, rifampicine etc.

Drugs eliminated through bile are reabsorbed in the intestine and once again reach the liver, where part of them:

- ▶ enters the general circulation,
- ▶ is metabolized,
- ▶ is once again removed through bile into the intestine

Enterohepatic circuit

Delays the elimination of drugs (eg. tetracycline, chloramphenicol, ampicillin, and other substances forming this circuit, maintaining therapeutically useful levels in the body).

Derivatives of: salicylic acid, tetrachlorides, halogenated, some antibiotics (tetracyclines), dyes, contrast agents etc. are excreted in bile.

The fact that most substances excreted in bile are reabsorbed and once again reach the liver will establish a double absorption circuit and elimination, known as gastro-entero-hepatic circulation.

Ions of: calcium, phosphorus, iron, salts of heavy metals are eliminated in the colon.

Insoluble drugs administered orally, which are not absorbed through the digestive tract (ex: Medicinal coal, paraffin oil, bentonites, kaolin, bismuth salts, magnesium sulfate, neomycin, streptomycin, digestive sulphonamides etc.) will be eliminated in feces.

In veterinary medicine there is a special case, of the anthraquinone purgatives, which are absorbed by the small intestine, but will be removed through the large intestine, through this segment's own circulation.

Elimination through the respiratory route

The alveolar surface, together with high pulmonary vasculature allow a rapid equilibration of the volatile agent from the blood and from the alveolar air.

Mostly gaseous substances are eliminated through the alveolar epithelium :

- ammonia,
- hydrogen sulphide,
- hydrocyanic acid,
- carbon dioxide,
- narcotic gas (eg: nitrous oxide, cyclopropane, ethylene),
- volatile anesthetics(eg: chloroform, ether, halothane, ethyl chloride),
- volatile oils (eg: oleum eucalipti, menthae, carvi, thymi, pini),
- alcohol,
- guaiacol,
- camphor and others.

- Some substances that are **partially** eliminated by the respiratory route are used in the treatment of pulmonary parasites.
- Drugs administered orally or parenterally, can **undergo metabolic processes** in the body which transform them into volatile substances that are eliminated via the respiratory route

- Some drugs can be partially oxidized in carbon dioxide and they are excreted by the respiratory route.
- In case that the carbon is radio-labelled, the excreted quantity can be measured this way.

Elimination through the skin

The dermal route may represent a significant excretion organ, which completes renal elimination.

Sweat glands (in species where they are present) and partly sebaceous glands represent the major routes of cutaneous elimination.

In general, cutaneous elimination is based on: **sweat hypersecretion** and less on **sebaceous secretion** (only important in sheep) having a:

favorable effect on the cutis and skin annexes (ex: antimycotics, sulfurs, arsenics etc.), but also:

unfavorable (ex: elimination dermatitis, produced in general by halogenated compounds).

Arsenics and sulfurs are eliminated through hair, skin appendages and stratum corneum.

Elimination through the mammary gland

Milk is a current food for humans.

Drug elimination in milk has a particular significance. The following substances are all eliminated through **milk**: chloroform, phenazone, lead, mercury and other heavy metals, caffeine, barbiturates, colistin, bromides and halogenated, phenylbutazone, cortisone, ether, camphor, substances that give milk an odor.

Excretion of radioactive metals can be a risk, as a consequence of nuclear accidents, which may contaminate pastures.

Cow milk

is usually weak acid (pH: 6,5-6,9) compared to the plasma (pH 7,2-7,4) and therefore tends to concentrate alkaline liposoluble drugs.

Most drugs are able to pass from plasma into milk = problems of toxicity in children.

Elimination through the egg

In birds some drugs diffuse:

- in the ovary and
- oviduct

being incorporated into eggs.

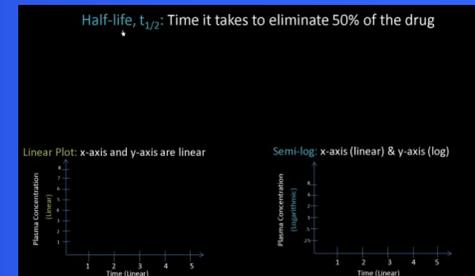
This phenomenon is reported for sulphamides.

Conclusions

The excretion of a drug will be fast when it or its metabolite in the blood are in ionized form, highly polarized, thus being poorly reabsorbed from tubular ultrafiltrate.

The excretion of weak acids or weak bases is influenced by the pH and the concentration differences at the level of the walls of renal convoluted tubules

The excretion of drugs is much accelerated by active transport systems.



Maintaining a **good blood supply** to the healthy kidney and, if not actively excreted, by the extent to which the drug is coupled to plasma proteins.

The end of drug action, is achieved by **metabolic inactivation and storage in the body**, away from the site of action and by simple excretion.

This process starts as soon as the absorbed drug enters the circulation.

Thank you for your attention!