Practice No. 5

Rodenticides

Rodenticides:

- Rodenticides are a group of pesticides which is primarily established for rodent control
- There are strict rules how, when and where to use them. In spite of this they are common source of both wild and domestic animals´ poisoning and are also used for malicious intentions to harm
- Poisoning is quite easy when baits with rodenticides are placed inconveniently at locations easily accessible for domestic animals esp. dogs and cats
- In these animals is also possible to poison themselves by eating a dead rodent which died of rodenticide poisoning – so called secondary poisoning

Division of rodenticides:

- according to chemical character:
  - inorganic – zinc phosphide (and other phosphides), formerly arsenic or thallium
  - organic – natural (strychnine, scilliroside, vitamin D), synthetic (anticoagulants)
- according to the route of administration: for eating, for drinking, for dusting, for fumigation
- according to the type of action: one dose, cumulative/repetitive intake

Zinc phosphide + aluminium phosphide

- Phosphides are the only inorganic and single-shot used agents nowadays. Their use is in agriculture, they are not allowed in households.
- They are very potent and absolutely non-selective and cause many accidental poisonings
- Zinc phosphide is used as feed bait and aluminium phosphide is fumigated in closed spaces (stocks, stores).
- Feed baits are made of grains impregnated by zinc phosphide or they are granules with active substance. Usually are not colourful!
- Often cause poisonings of wild animals (pheasants, eagles, hares etc.) because they are used outdoors on fields

Metabolism:

- In acid environment of stomach zinc phosphide easily and quickly hydrolyses and releases gas phosphane (PH_3), which is the real toxic agent
- Aluminium phosphide is decomposed by air humidity (thus used by fumigation), so pure gas phosphane is inhaled in the poisoning by this substance

Mechanism of action:

- This gas easily crosses all barriers and is absorbed into blood and cells
- Inside of the cells it blocks oxidative phosphorylation and energy production, and increases free oxygen radicals which damage the cells
- First it affects stomach mucosa cells and causes irritation, inflammation and necrosis of mucosa

- Then it goes to blood and damages veins (endothelium), which leads to increased permeability and fluid loss, and later all organs. Mainly liver, kidneys, heart and later brain are affected.
- When inhaled it causes immediate lung oedema
- Intoxication is acute or peracute and prognosis is often malignant because of irreversibility of such multiple damage

Clinical signs:

- nausea, vomiting, bloating, severe colic with bloody excrements, animal is rapidly weakening and dies within a few hours
- the speed and severity of clinical signs depend on the stomach content before the bait was ingested

Pathological examination:

- gastritis + enteritis with haemorrhages and necrosis, GIT content smells like **garlic** !!! Petechias and other types of bleedings on serosas, brain, endocardium. Parenchymatic organs are dystrophic

For laboratory examination GIT content or vomits are used. They must be immediately stored in a closed glass bottle or in a plastic container, and preferably frozen!!!

Treatment:

- First aid - emetics, activated charcoal, and then neutralise HCl in stomach (give baking soda). Further treatment if many organs are already damaged is usually ineffective but you may try it symptomatically. Fluid therapy and glucose are given.

Cholecalciferol – vitamin D3

- Cholecalciferol is so called antirachitic vitamin
- It increases intestinal absorption of calcium, decreases it excretion, and mobilises it from bones (osteolysis) which results in hypercalcaemia
- Hypercalcaemia lasting for more then a few minutes is dangerous, so the body tries to quickly store calcium elsewhere. In overdose the re-deposition into bones is a too slow process, so calcium from blood is then deposited in other organs and structures, especially in vein walls and kidneys. The results are fragility of veins and kidney failure.
- Rodents and cats are mainly susceptible to this poisoning. Damage in other animals is not so quick, but juvenile dogs and horses are also quite sensitive to it
- Even if therapy of poisoning is successful, damage of kidneys can cause problems for many months and sometimes it lasts for the rest of the animal's life
- Often chronic poisoning not from a rat bait, but as an overdose of food supplements

Clinical signs:

- anorexia, haematemesis, diarrhoea with signs of blood in excrements, ataxia, lethargy, bradycardia; hematuria, anaemia, polyuria and polydypsia due to kidney damage, in final stages neurological symptoms from uraemia

Pathological examination:

- Calcification and damage of kidneys, veins, eventually other organs, exostosis

Treatment:

- If found early - emetics or gastric lavage, activated charcoal
- For a quite long period (three - four weeks) we must increase calcium elimination by administration of fluids, diuretics and in cats sometimes also corticosteroids
- Animals must be kept in calm and in shadowy place to avoid exposition to sunlight (activates cholecalciferol formation in skin of mammals and birds)

Scilliroside

- It is a cardiotoxic glucoside found in a plant called *Scilla maritima* (sea onion)
- Cardioactive glucosides have enterohepatic cycling
- It has been used since ancient times as a powder made from bulbs
- For animals with vomiting reflex this natural product is quite safe due to content of emetin, which causes tenacious vomiting and prevents absorption of higher doses of scilliroside to the organism
- In USA and some countries pure scilliroside is used, so no protection of emetin presence and toxicity to all species of animals must be expected

Mechanism of action:

- all cardioactive glucosides inhibit myocardial form of the enzyme Na/K ATPase, which leads to the cummulation of Na^+ inside of muscle cells and their stimulation to prolonged contraction

Clinical signs:

- changes of heart rhythm, which are serious and can lead to death
- nausea, diarrhoea, ataxia, fainting, bradycardia, cyanosis

Treatment:

- emesis, gastric lavage, repetitive doses of activated charcoal, administration of antiarrythmic agents, fluid therapy, oxygen inhalation

Anticoagulative rodenticides

- Most often used rodenticides nowadays
- Derived from a natural substance – coumarin, found in plants, mainly in sweet clover (*Melilotus officinalis*)
- Right now synthetic substances divided into three groups:
  - coumarine derivates of the first generation (warfarin)
  - coumarine derivates of the second generation (e.g. bromadiolone, brodifacoum)
  - indandione derivates (e.g. chlorophacinone)
- Often cause intoxications in domestic animals and are used intentionally to cause harm
- First generation works on a cumulative principle, second one and indandiones are usually single-shot agents
- Second generation and indandiones undergo enterohepatic cycling

Mechanism of action:

- All generations work by the same mechanism of action, only their chemical structure and metabolism in the body is different
- Coumarines are very similar to vitamin K and compete with it on hepatocyte receptors
- Several factors of blood coagulation are produced in liver in an inactive form. Activation is done by carboxylation in the presence of vitamin K as a co-factor
- Vitamin K must be in active quinone form for this reaction. After carboxylation vitamin K changes to inactive, epoxide form
- To transform it back to quinone, we need an enzyme epoxide-reductase
- Coumarines bind to this enzyme and block the cycle of vitamin K changes increasing amount of inactive clotting factors in blood, and haemostasis worsens
- Chronic exposition leads also to direct damage of veins - increased fragility

Clinical signs:

- first phase - spontaneous bleeding from nose (epistaxis), mouth, anus; weakness, sleepiness, apathy, haematuria and melena (black excrements with digested blood), anaemia, long bleeding after the slightest injury, weak pulse, low body temperature
- second phase – spontaneous subcutaneous bleeding, bleeding to muscles, body cavities = haemorrhagic diatesis. Animals die due to hypovolaemia and anaemia

Factors that worsen intoxication:

- physical activity, hard and rough diet

Pathological examination:

- multiple haematomas, haemothorax, haemoperitoneum, anaemia of body organs; blood not coagulated, of red colour even after death

Laboratory examination:

- Intravital or post mortem samples of tissues, GIT content, blood, urine and the rests of food or bait:

- Liver, urine, bait and stomach content/vomits are analysed for the presence of poisonous substance by chromatographic methods
- In blood we perform so called Quick test (PT). It measures prothrombine time in blood plasma - a time after which the blood with citrates – block coagulation by binding Ca^{2+} – coagulate after the addition of calcium and thromboplastine
- Physiological time for dogs and cats is about ten seconds, pathological one hundred and more
- Also it is possible to do PIVKA test, which measures the concentration of inactive clotting factors in blood

Treatment:

- Keepers often come quite late - first signs of poisoning are very mild and non-specific: first aid is useless
- Administer vitamin K1 as a direct antidote for at least 2 weeks (first generation) or five weeks (second generation + indandiones)!
- Administer it s.c. to avoid another massive bleeding. After hospitalisation, it can be also administered p.o.
- Activated charcoal must be administered repetitively for one week
- In critical cases, blood transfusion is also possible
- Keep animal in calm, give fluid diet (in ruminants grains, not hay)
- Don't use trappings etc.

Beware of other medicaments which can increase bleeding and decrease coagulation (aspirin and other non-steroid anti- inflammatory drugs, corticosteroids, sulphonamides, furosemide etc.)

Practical work: Assessment of anticoagulative rodenticides in liver samples by TLC
Measurement of Quick test