Common Poisonings in Small Animals Mini Series

Session Three: Pick 'n' Mix of Other Common Poisons

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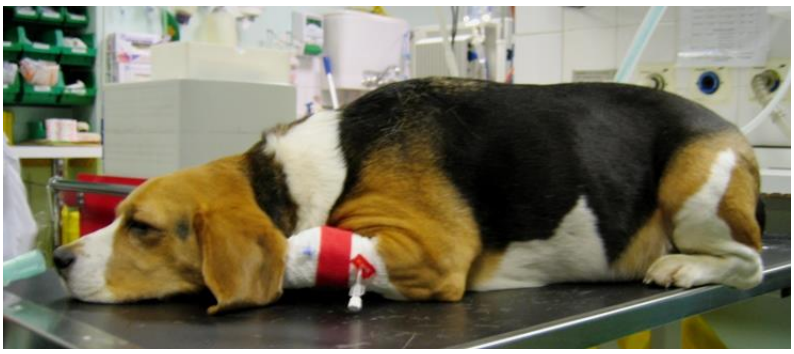

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Other Common Small Animal Poisons

Paracetamol (Acetaminophen)

Acetaminophen (paracetamol in the United Kingdom) is used extensively by people and is widely available over-the-counter. It is contained in a variety of preparations either solely or in conjunction with other drugs including aspirin and opioids. It is an antipyretic and analgesic agent. Acetaminophen has been used therapeutically in dogs but **should not be administered to cats**.

Excessive canine and feline exposure to acetaminophen typically occurs either as a result of accidental ingestion (most common in dogs) or due to misguided 'therapeutic' administration by owners (most common in cats).

Toxic dose

A dosage of 100-200 mg/kg has been reported to cause clinical signs in dogs although higher dosages may be required and occasionally signs are seen with lower dosages. Cats are much more sensitive and signs of poisoning are generally seen at 50-100 mg/kg but may occur with dosages as low as 10 mg/kg.

Toxicokinetics

Acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract and undergoes hepatic metabolism. In dogs low doses of acetaminophen are predominantly metabolised via capacity-limited glucuronidation and sulphation. This produces non-toxic metabolites that are excreted in bile and urine. However any metabolism (oxidation) via the cytochrome P450 pathway produces *N*-acetyl-para-benzoquinoneimine (NAPQI) that is highly reactive and toxic.

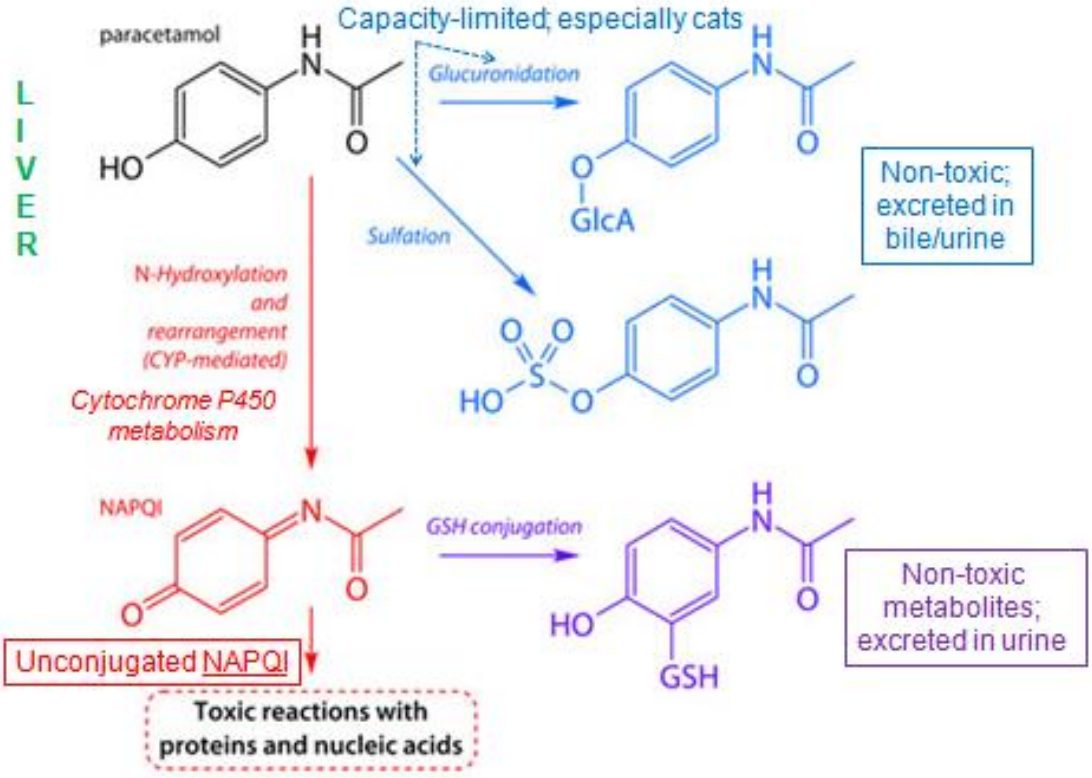
NAPQI is usually conjugated with cellular glutathione to produce non-toxic metabolites that are excreted in urine. As the dosage of acetaminophen increases a greater proportion undergoes metabolism via the cytochrome P450 pathway (due to saturation of the glucuronidation and sulphation pathways) resulting in greater production of NAPQI. Glutathione stores, especially in the liver and red blood cells, are subsequently exhausted resulting in higher concentrations of toxic unconjugated NAPQI. At higher doses acetaminophen also inhibits glutathione synthesis further compromising this metabolic pathway.

Cats are less able to metabolise acetaminophen via glucuronidation (and sulphation) and the end result is greater metabolism via the cytochrome P450 pathway and an increased susceptibility to poisoning compared to dogs.

Mechanism of toxicity

Glutathione is important in protecting cells from oxidative injury and depletion of glutathione by conjugation with NAPQI makes cells susceptible to oxidative damage. In dogs **hepatocellular** oxidative injury and necrosis is most common with consequent liver failure possible.

In cats **red blood cells** are most susceptible with Heinz body formation, methaemoglobinaemia and haemolytic anaemia possible. Feline haemoglobin is more prone to oxidation than canine haemoglobin. As methaemoglobin is unable to transport oxygen, methaemoglobinaemia compromises oxygen-carrying capacity causing tissue hypoxia and characteristic muddy brown mucous membranes. Glutathione, deficient in these cases, is also required to reduce methaemoglobin to haemoglobin.



Clinical signs

In dogs clinical signs usually relate to hepatotoxicity and include vomiting, anorexia, abdominal pain and icterus. Methaemoglobinaemia may be seen with higher exposures resulting in muddy/chocolate brown or cyanotic mucous membranes. It is unusual for methaemoglobinaemia to occur in dogs without subsequent signs of hepatotoxicity but this has been reported. Mucous membranes may also be pale due to anaemia secondary to intravascular haemolysis. Oedema of the face and/or paws may also be identified. Neurological signs may be present with severe liver dysfunction and hepatic encephalopathy and are also potentially associated with severe methaemoglobinaemia.

In cats the most common clinical signs are muddy brown, cyanotic or pale mucous membranes, oedema of the face (especially mandibular region) and/or paws, and respiratory compromise; vomiting, depression, hypothermia and pruritus may also occur. Neurological signs may be present with severe methaemoglobinaemia and coma is associated with poor prognosis. Icterus may occur and at lower exposures is predominantly the result of red blood cell lysis. Clinically significant hepatotoxicity may be seen at higher exposures.

Both hepatic and erythrocyte-associated poisoning syndromes have been reported in both dogs and cats. Clinical signs usually develop within 4-24 hours of exposure; liver enzymes typically start to increase within 24 hours of exposure.

Methaemoglobinaemia is confirmed definitively by measurement using co-oximetry. However this is not widely available. Nevertheless its presence can be inferred by putting a drop of the blood on filter paper; the filter paper stains brown and does not change colour. Alternatively, oxygen can be bubbled through a tube of the blood; if significant methaemoglobinaemia is present, oxyhaemoglobin does not form and the blood will not turn red.

Case management

The aims of treatment for acetaminophen poisoning are:

- Minimise further acetaminophen absorption with routine GID
- Promote elimination of unmetabolised acetaminophen
- Minimise NAPQI formation
- Supplement glutathione precursors to protect cells and encourage NAPQI elimination
- Provide oxygen supplementation
- Provide supportive therapy as required – fluid therapy, oxygen-carrying support, whole blood/fresh frozen plasma for coagulopathy, other treatment for liver failure

Antidote therapy:

Acetaminophen is one type of poisoning for which specific antidote therapy is available and treatment is recommended even if there is a significant delay in institution as a successful clinical outcome may still be obtained.

N-acetylcysteine:

N-acetylcysteine is rapidly hydrolysed to cysteine in vivo that is required for intracellular glutathione synthesis. N-acetylcysteine administration thereby attempts to address cellular glutathione deficiency. Glutathione itself cannot be used therapeutically as it is not readily taken up by cells. N-acetylcysteine also acts directly on NAPQI facilitating its excretion and is oxidised to sulphur in the liver increasing the capacity of the sulphation pathway. N-acetylcysteine can be given intravenously or per os if the patient is not vomiting. Intravenous administration is more patient friendly and oral administration may cause nausea or vomiting; the product is also reported to taste unpleasant and concurrent activated charcoal administration will reduce absorption from the gut. Some humans suffer an anaphylactoid reaction following intravenous administration (the incidence is perhaps around 8-10%); to the author's knowledge this has not been recognised in dogs or cats thus far or at least not at a similar incidence. The oral route may seem more intuitive give that it will be absorbed into the portal circulation which flows to the liver and that is where the toxicity occurs. The oral preparation is also cheaper but most practices are likely to only stock the injectable preparation.

In human medicine there have traditionally been two different NAC treatment protocols – a 20-hour IV protocol or a 72-hour oral protocol. However there is some debate about the validity of this, e.g. in some patients 72 hours is excessive, in others 20 hours is too short even if the IV route is used. It probably makes more sense to titrate therapy in individual cases based on measuring plasma acetaminophen levels – which they do routinely in human patients – and liver transaminases. In veterinary medicine various treatment protocols have been reported, typically not varying regardless of which route is used. The one below is the most commonly recommended.

If N-acetylcysteine is not available, or in severe cases of poisoning, additional sources of sulphur donors may be used. S-Adenosylmethionine (SAMe) is one such product that may also have other additional beneficial effects. The use of cimetidine has been recommended in acetaminophen poisoning. This agent can inhibit cytochrome P450-mediated oxidation and may therefore reduce the formation of NAPQI. Given this mechanism of action, cimetidine would need to be given very early on to be effective and is considered an adjunctive therapy only.

N-acetylcysteine	D, C: initial loading dose of 140 mg/kg i.v.; further 5-7 doses of 70 mg/kg i.v. q 6 h	Rapidly hydrolysed to cysteine in vivo that is required for intracellular glutathione synthesis; glutathione conjugates NAPQI Administer intravenously undiluted or diluted in a 5 % glucose solution Oral administration possible if not vomiting but not particularly patient-friendly, may cause nausea and vomiting

S-Adenosylmethionine (SAMe)	D: initial dose of 40 mg/kg p.o.; then 20 mg/kg p.o. q 24 h for 9 days C: 180 mg (total dose) p.o. q 12 h for 3 days; then 90 mg p.o. q 12 h for 14 days	Feline protocol has only been reported experimentally
Cimetidine	D, C: 5 mg/kg slow i.v. q 8 h	Administer as early as possible for greatest efficacy

Methaemoglobin reduction:

In addition to the above therapy, treatment designed to reduce methaemoglobin to haemoglobin may be administered. Methylene blue has been employed here but is typically not readily available. It is an interesting agent because it can both reduce methaemaglobin (Fe^{3+}) to haemoglobin (Fe2+) and if too much is given actually oxidise haemoglobin to methaemaglobin! Other adverse effects include Heinz body anaemia and reduced red cell lifespan due to red cell oxidative injury. Cats are especially sensitive and its use in this species is typically not recommended.

However **ascorbic acid (vitamin C)** may be used and oral preparations can usually be easily obtained. Poor compliance may preclude administration in cats. The author has administered ascorbic acid in drinking water to dogs that were not vomiting. Preparations of ascorbic acid for intravenous use are available and the treatment regime is the same as for oral preparations.

Ascorbic acid (Vitamin C)	D, C: 30 mg/kg p.o. q 6 h for 6 doses	Preparations for intravenous use may be available; treatment regime as for oral preparations

The prognosis in acetaminophen poisoning is guarded and depends on the dosage of acetaminophen absorbed and the delay before institution of antidotal therapy. Aggressive early intervention is recommended. No long-term residual pathology is thought to occur in patients that do recover.

Vitamin K Antagonist Anticoagulant Rodenticides

Anticoagulant rodenticides usually contain derivatives of either 4-hydroxycoumarin (e.g. brodifacoum, bromadiolone, difenacoum) or indane-1,3-dione (e.g. diphacinone, chlorphacinone). These preparations have a variable potency and duration of action that may be related to the generation type of the constituent compound. Second generation compounds are typically longer-acting and have largely replaced older first generation ones. A variety of different commercial preparations are available.

Anticoagulant rodenticide poisoning in dogs is usually primary (direct ingestion of rodenticide) but clinically significant secondary poisoning due to ingestion of poisoned rodents has also been reported. Cats are presented only rarely with rodenticide intoxication.

Toxic dose

Given the large number of anticoagulant rodenticide substances in use it is beyond the scope of these notes to detail toxic doses for each individual substance and the reader is recommended to consult other texts or a veterinary poisons database.

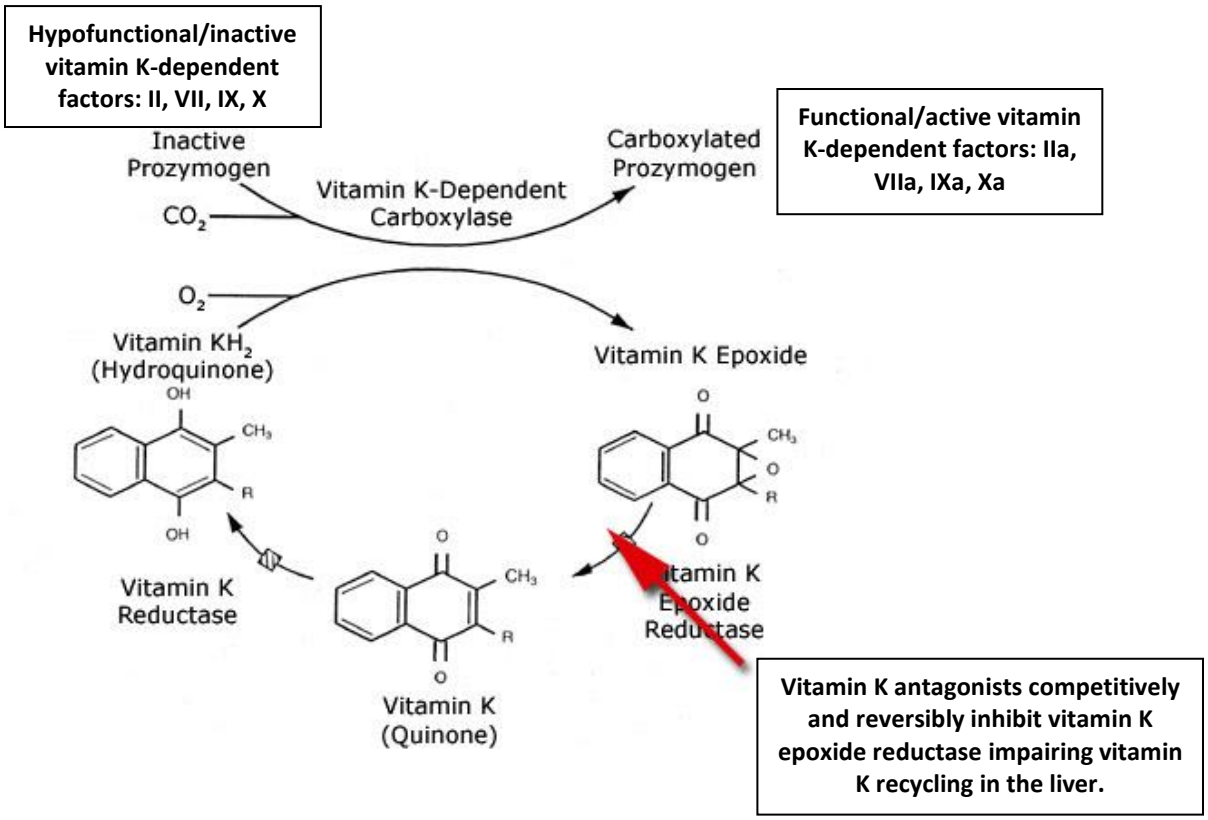
Toxicokinetics

Anticoagulant rodenticides are generally absorbed slowly but substantially from the gastrointestinal tract. A long plasma half-life potentially of a number of days is typical, and duration of action can be very prolonged even up to several weeks in some cases. These compounds undergo slow metabolism by hepatic microsomal mixed-function oxidases to form inactive metabolites that are excreted in urine or bile.

Mechanism of toxicity

Vitamin K_1 hydroquinone is required for the conversion of inactive precursor coagulation factors to their active forms. During this conversion vitamin K_1 hydroquinone is oxidised to vitamin K_1 epoxide. Following absorption anticoagulant rodenticides inhibit hepatic vitamin K_1 epoxide-reductase which is partially responsible for the conversion of vitamin K_1 epoxide back to vitamin K_1 hydroquinone. Anticoagulant rodenticides therefore impair vitamin K_1 'recycling' by the liver leading to its depletion as existing stores are exhausted; they thereby prevent conversion of several inactive coagulation factors to their active forms. The vitamin K_1-dependent coagulation factors are factors II (prothrombin), VII, IX and X.

Anticoagulant inhibition of vitamin K_1 epoxide-reductase is essentially competitive and reversible; therefore administration of exogenous vitamin K_1 acts therapeutically to reduce inhibition.



A delay in the onset of clinical signs following anticoagulant rodenticide ingestion is usually seen. This is due to the presence of circulating active vitamin K-dependent coagulation factors that must be exhausted for clinical signs to become apparent. Of the vitamin K-dependent factors, factor VII has the shortest plasma half-life. This factor is traditionally classified as part of the extrinsic coagulation pathway that is evaluated using the prothrombin time (PT). This explains the early clinical usefulness of measuring PT in cases of suspected anticoagulant rodenticide poisoning.
Activated partial thromboplastin time (APTT) and activated clotting time (ACT) are used to evaluate the intrinsic (includes factors II, IX and X) coagulation pathway and are expected to become prolonged subsequently also.

Clinical signs

Clinical signs usually develop within 1-7 days of exposure and may persist for more than 2 weeks without intervention; visible clinical signs may not be apparent even though PT is prolonged. Clinical signs reflect bleeding tendency as described above and may be accompanied by a variety of non-specific signs such as lethargy, depression and reduced appetite. Anticoagulant rodenticide poisoning may manifest with signs of respiratory distress, most commonly due to haemothorax but also secondary to pulmonary haemorrhage, and coughing (including haemoptysis) is reported. Bleeding into the peritoneal cavity and mediastinum is also reported. There may be evidence of external bleeding – for example nasal or gingival – and gastrointestinal haemorrhage may manifest as melaena, haematemesis and abdominal pain. Petechiae, ecchymoses and excessive bleeding at venepuncture sites may be identified. Bleeding in other sites will manifest with expected clinical signs – for example lameness secondary to bleeding into joints or neurological signs secondary to central nervous system haemorrhage.

In animals that have become anaemic secondary to blood loss anticipated physical examination findings such as pale mucous membranes, tachycardia and hyperdynamic pulse quality will be present. If blood loss is considerable and rapid, evidence of hypoperfusion secondary to hypovolaemic shock may be identified.

Laboratory and Other tests

As mentioned above, there is a lag period following anticoagulant rodenticide ingestion of at least a day but usually 2-3 days before clinically significant coagulopathy develops. Clotting times and haematocrit/total solids would not therefore be expected to be abnormal in dogs presenting with very recent exposure.

In any animal presenting with suspected anticoagulant rodenticide poisoning a baseline minimum database should be established. This should include manual packed cell volume, plasma total solids, peripheral blood smear, and **coagulation profile (in particular PT)** taken before initiation of therapy (see below). Prothrombin time is prolonged first in poisoned patients as factor VII becomes depleted earliest but prolongation of APTT and ACT usually also occurs before the onset of clinical signs.

Peripheral blood smear should be evaluated for platelet count and where anaemia is identified, for evidence of regeneration. Mild to moderate thrombocytopenia is a common finding. Lack of a regenerative red blood cell response may represent preregenerative (as opposed to non-regenerative) anaemia; it usually takes at least 3 days in dogs, often longer in cats, for regeneration to be detected on blood smear examination following haemorrhage. Blood typing may also be appropriate. Low serum total solids are expected in anaemia secondary to blood loss.

Thoracic and abdominal diagnostic imaging may identify major sites of haemorrhage with the thoracic cavity being the most common site of bleeding. Thoracocentesis and abdominocentesis will likely reveal a non-clotting sanguineous effusion with packed cell volume similar to that of the patient's peripheral blood.

Treatment

1. Initial priority:

Routine gastrointestinal decontamination including activated charcoal use is the priority in dogs presenting within an appropriate timeframe. The lag period following ingestion before clinical signs develop means that by the time a patient is showing clinical signs the poison will no longer be present in the GI tract and GI decontamination is therefore of no use.

In dogs that present with haemorrhage, the initial priority is to correct perfusion deficits with intravenous replacement isotonic crystalloid. Fresh whole blood is unlikely to be available in the necessary timeframe for correcting haemorrhagic hypovolaemia but packed red cells should be administered if anaemia is clinically significant or becomes moderate-to-severe including as a result of dilution.

Subsequently fresh frozen or stored frozen plasma should be administered to replace clotting factors, correct coagulopathy and prevent on-going haemorrhage.

If the patient is dyspnoeic as a result of clinically significant haemothorax, thoracocentesis is necessary; ideally aim to only remove the minimum volume necessary to improve respiratory status sufficiently as the remainder should be absorbed over the following hours/days. Haemothorax is generally not drained unless it is thought to be responsible for dyspnoea that is too severe as the effusion will be resorbed in time thereby reducing the amount of red cells that the patient loses. Furthermore performing thoracocentesis to drain haemothorax in a coagulopathic dog contains additional risks and should only be considered if the dyspnoea is severe. Potential secondary complications of having blood in the pleural space for a few days are infection and a retained fibrohaemothorax causing lung restriction; in humans the former is considered rare and the latter even rarer – to the author's knowledge there is no veterinary data available on this.

2. Antidotal therapy:

Once the dog's perfusion is improved, antidotal vitamin K therapy is essential to allow regeneration of vitamin K-dependent clotting factors. Although vitamin K therapy is essential, it will not act quickly enough in patients with clinically significant haemorrhage to correct coagulation abnormalities and stop the bleeding – hence the other measures described are more important in the first instance.

Asymptomatic:

In asymptomatic patients prothrombin time should be measured and no additional therapy is required if PT is within normal limits. Repeat testing of PT should be performed within 2-3 days. If a significant delay in obtaining the results of this test is unavoidable it may be appropriate in individual cases to commence antidotal therapy with synthetic vitamin K_1 (phytomenadione) once blood sampling has been performed and to discontinue therapy if normal results are subsequently obtained.

If vitamin K_1 therapy is commenced a significant period of time prior to sampling for testing of PT, subsequent results may be affected and a definitive diagnosis of coagulopathy secondary to rodenticide poisoning cannot be established. Subsequent vitamin K_1 therapy in these cases should then be managed as recommended for animals presenting with clinical signs of haemorrhage or with prolongation of prothrombin time.

Symptomatic:

If symptomatic at presentation or asymptomatic but PT prolonged (or significant delay anticipated in obtaining PT), administer 2-5 mg/kg of vitamin K_1 daily divided into 2-3 doses. New veterinary-licensed preparation from Dechra (Eurovet) licensed for intravenous use. Other preparations should be given subcutaneously at multiple sites using the smallest possible needle. Preferably continue parenteral administration until PT normalises then change to oral administration at same daily dose, i.e. 2-5 mg/kg daily divided into 2-3 administrations.

Vitamin K_1 therapy should typically be continued for 2-6 weeks depending on the type of anticoagulant ingested (second generation compounds typically require a longer course of vitamin K_1 therapy). If the type of anticoagulant is unknown, a 2-week course of treatment is reasonable. After this time PT is rechecked and treatment discontinued as long as PT is normal. Prothrombin time is rechecked 2-3 days after stopping treatment:

- No further treatment is required if PT is normal
- If PT is prolonged, vitamin K_1 therapy should be restarted and continued for a further 7 days before repeating the above process
- Persistent PT prolongation or recurrence of spontaneous haemorrhage may suggest repeat exposure

Animals with evidence of haemorrhage at presentation secondary to rodenticide ingestion will have PT prolongation. Nevertheless it is essential to test PT at presentation both to support the presumptive diagnosis and to allow monitoring of response to therapy.

As with any severe coagulopathy animals showing signs of haemorrhage secondary to suspected rodenticide poisoning should be handled gently, subjected to minimum stress and undergo exercise restriction. Venepuncture should only be performed using peripheral veins and with the smallest needle possible; adequate prolonged pressure should be applied to the site following sampling.

Prognosis

Prognosis is generally good with adequate and timely treatment but is partly dependent on site and severity of haemorrhage at time of presentation. It obviously also depends on whether transfusion of blood products is possible in cases in which haemorrhage is significant.

Rodenticides containing Vitamin D

Some rodenticide preparations contain vitamin D compounds and can cause vitamin D toxicity; they may also contain anticoagulant agents as well

Vitamin D toxicity

Sources

Vitamin D compounds include calciferol (ergocalciferol, vitamin D2), cholecalciferol (cholecalciferol, vitamin D3), calcipotriol and calcitriol amongst others. Potential sources include:

- Vitamin preparations
- Human medicines – especially psoriasis creams
- Cod liver oil
- Veterinary medicines
- Growth promoters
- **Some rodenticide preparations – may contain anticoagulants as well**

Toxicology

Toxic dose:

Varies depending on form of vitamin D involved, e.g. in mature dogs:

- Cholecalciferol: 2 mg/kg (80,000 IU/kg)
- Calcipotriol: 50 **µ**g/kg

As shown by these doses, newer compounds or analogues (e.g. calcipotriol) generally more toxic than parent compounds (e.g. cholecalciferol)
Puppies and cats in general more susceptible; also animals with predisposing conditions, e.g. renal disease

Toxicokinetics:

Rapid absorption
Hepatic metabolism
Calciferol/cholecalciferol metabolised to calcitriol (1,25-dihydroxycholecalciferol) which induces hypercalcaemia

Mechanism of toxicity:

Hypercalcaemia via increased intestinal calcium absorption, increased renal calcium reabsorption and enhanced bone resorption
Causes nephrotoxicity and potentially widespread tissue calcification
Hyperphosphataemia also consistently present

Clinical signs

Clinical signs of hypercalcaemia (and concurrent hyperphosphataemia) most commonly associated with neurological (e.g. ataxia, twitching), cardiovascular and gastrointestinal (e.g. vomiting, diarrhoea) systems and with the kidneys
Depending on the preparation consumed signs may be seen 6-48 hours post-ingestion

Clinical evaluation

In emergency setting, diagnosis is suspected based on ionised and total hypercalcaemia + possible exposure to vitamin D-containing preparation

(Specific diagnosis involves measuring serum intact PTH – should be suppressed – and vitamin D compounds/analogues – but diagnosis can be challenging/impossible)

Treatment

Treatment should be appropriately aggressive and involves:

- Gastrointestinal decontamination including activated charcoal use if still appropriate
- Close monitoring of electrolytes, renal parameters and hydration
- Symptomatic and supportive care including possible antiemetic and gastroprotectant use
- Treatment for hypercalcaemia:
    - Promoting calciuresis using intravenous 0.9% sodium chloride (normal saline) and furosemide
    - Corticosteroid therapy to suppress bone resorption, reduce intestinal calcium absorption and promote calciuresis
    - Possible additional use of salmon calcitonin (rapid onset but short-acting effects to counter hypercalcaemia; likely multifactorial effects but remains unclear)
    - Possible treatment with a bisphosphonate drug (slower onset of action; inhibits bone resorption)

Prognosis

May have severe morbidity
Good if treatment started before hypercalcaemia develops
Guarded if signs severe at presentation or presentation delayed
Poor if tissue calcification has already started to occur

- Death may be from irreversible kidney failure or lung mineralisation and haemorrhage

Grave if haematemesis present (suggests severe gastric ulceration)

Xylitol

Xylitol poisoning reported in DOGS; no published reports of feline poisoning

Sources

Naturally-occurring sugar alcohol found in low concentrations in various fruits and vegetables

Extracted commercially and used extensively:

- As a sweetener in low carbohydrate/low glycaemic index/diabetic products, e.g. baked goods, baking powder, tomato sauce, honey, jam, chocolates etc.
- Reduces dental caries formation so increasingly used in various chewing gums, sweets, toothpastes and other oral care products
- Also found in some prescription drugs, including veterinary ones (e.g. Metacam®), as well as some vitamins and nutritional supplements

Manufacturers are not obliged to specify the xylitol content of products in all cases and sometimes only the total sugar alcohol content (including e.g. sorbitol, isomalt) is listed.

Toxicology

Toxic dose:

Significant **hypoglycaemia** from more than 100 mg/kg (but mild signs may occur at lower doses and some recommend decontamination even at 50 mg/kg)

Hepatotoxicity: some references suggest doses greater than 500 mg/kg may be associated with hepatic injury. BUT it remains unclear whether hepatotoxicity is dose-dependent or in fact idiosyncratic (i.e. non-dose dependent). As such, given that liver failure can be fatal, a cautious and aggressive approach to decontamination is recommended.

Toxicokinetics:

Excessive exposure via ingestion
Absorption in dogs is rapid and almost complete (peak plasma levels possible within 30 minutes)

- Slow release from ingested foodstuffs or chewing gum may delay absorption and explain potentially delayed onset and/or sustained hypoglycaemia seen in some dogs

Metabolism predominantly hepatic, rapid
Virtually no urinary excretion

Mechanism of toxicity:

Potent and dose-dependent stimulation of pancreatic insulin release in dogs.

Insulin release may cause:

- HYPOGLYCAEMIA – can be severe, also delayed and/or sustained
- Hypokalaemia
- Hypophosphataemia

HEPATIC INJURY and probable acute hepatic necrosis (mechanism(s) not yet fully understood):

- Sufficient injury results in hepatic insufficiency/failure
- Coagulopathy is one potential consequence
- Severe liver failure may also cause hypoglycaemia (more delayed onset than that due to insulin release)

Clinical signs

Dogs that develop hypoglycaemia do not necessarily go on to develop liver failure Dogs with liver failure do not necessarily have hypoglycaemia initially

Hypoglycaemia:

Signs often within 1-2 hours of ingestion
Speed of onset depends on e.g.

- Specific source in terms of how quickly it disintegrates to release xylitol in the gastrointestinal tract (e.g. mints more quickly than chewing gum).
- Degree of mastication before ingestion (e.g. dogs usually do not chew gum before swallowing it); as such when chewing gum is the source, onset of signs may be delayed for up to 12 hours.

Signs include:

- Lethargy
- Weakness
- Vomiting
- Ataxia
- Altered mentation from depression through to coma
- Seizures

Hepatic injury/failure:

Signs more delayed in onset (up to 72 hours after exposure); typical signs of liver failure

Coagulopathy may manifest as petechiae/ecchymoses, haemorrhagic faeces, and excessive bleeding from venepuncture sites.

Clinical evaluation

Blood glucose:

Regular monitoring (e.g. every 2 hours for the first 12 hours) is recommended even in dogs that are normoglycaemic at presentation

May be normal or mildly to severely reduced depending on timeframe since ingestion
Occasionally hyperglycaemic initially which progresses to hyperglycaemia

- More sustained hyperglycaemia may be a result of the Somogyi phenomenon (rebound hyperglycemia) that occurs with insulin overdose

Liver evaluation:

Baseline liver enzymes may be re-evaluated 12, 24 and 48 hours later and clotting times assessed if liver enzymes are elevated.

Liver enzymes and coagulation tests expected to be within normal limits in dogs presenting shortly after exposure. Establishing *baseline parameters* at presentation is important to facilitate on-going monitoring.

- Mild elevations in liver enzymes may be seen early, even within 4 hours of ingestion; however based on evidence available thus far, this does not necessarily mean that the patient will develop significant liver injury and failure.

Hepatotoxicity may reveal marked increase in serum alanine transaminase (ALT) activity, mild to moderate increase in serum alkaline phosphatase (ALP) activity, and hyperbilirubinaemia.

- Going forward other evidence of hepatic dysfunction (e.g. hypoglycaemia, hypoalbuminaemia) may be seen

Coagulation:

Prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) may be detected
In dogs with elevations in liver enzymes, regular monitoring of clotting tests is recommended for 3-4 days following exposure
NB. Mild to moderate thrombocytopenia is also commonly reported although typically not severe enough as to induce spontaneous haemorrhage.

Others:

Early insulin-induced hypokalaemia, hypophosphataemia

Hyperphosphataemia may occur later, being associated with subsequent hepatic damage and *may be* a poor prognostic indicator.

Treatment

With it still being unclear whether hepatotoxicity is or is not dose-dependent and given the potential for fatal acute hepatic failure, decontamination is recommended in all cases.

Routine gastrointestinal decontamination indicated in appropriate cases:

- Emesis should not be induced in dogs with marked neurological compromise secondary to hypoglycaemia
- Some dogs may already have self-decontaminated through vomiting prior to presentation
- Activated charcoal may be administered empirically; may have limited/no benefit due to rapid xylitol absorption. A report of in vitro evaluation also suggests that xylitol binds poorly to activated charcoal.

Hypoglycaemia: standard parenteral and possibly oral glucose supplementation; may need to be both aggressive and prolonged.

- Regular small meals and possible oral sugar supplementation may be sensible in asymptomatic dogs
- Asymptomatic normoglycaemic dogs should nevertheless be hospitalised for at least 12 hours post-ingestion due to the possibility of delayed-onset hypoglycaemia, especially when chewing gum is the source.

Coagulopathy secondary to hepatic dysfunction: fresh frozen plasma (FFP) and vitamin K_1. As with any severe coagulopathy:

- Gentle handling
- Minimum stress
- Exercise restriction
- Venepuncture using peripheral veins ideally, with the smallest needle possible; apply adequate prolonged pressure to site following sampling

Empirical use of antioxidant **hepatoprotectants** (e.g. S-adenosylmethionine (SAMe), N-acetylcysteine, silymarin) probably warranted although beneficial effect not been established.
Treatment for possible hepatic encephalopathy (e.g. ampicillin and lactulose) with severe liver failure
Treatment otherwise supportive and symptomatic

Prognosis

Hypoglycaemia only: generally good with timely and appropriate management

- Likely to be worse if repeated bouts of hypoglycaemia, especially when associated with central nervous system signs; CNS injury from neuroglycopenia possible

Prognosis worse with sustained elevations in liver enzymes; guarded to poor with evidence of hepatic dysfunction; grave for acute hepatic failure

- Hyperphosphataemia may be a poor prognostic sign for survival; however, even some of these severely affected dogs have successfully recovered

Survival from xylitol poisoning may not be correlated with exposure dosage

Baclofen

Sources

Baclofen poisoning is clinically most likely to be seen in DOGS but cases in cats have been reported
Usually oral exposure due to ingestion of owner's tablets; available as 10 mg and 20 mg tablets

Baclofen (4-amino-3(p-chlorophenyl)-butanoic acid) is a centrally-acting skeletal muscle relaxant
Used in people for multiple sclerosis (relief from flexor spasms, concomitant pain, clonus, and muscle rigidity); cerebral palsy; also used in spinal cord injuries and other spinal cord diseases
Used to decrease urethral resistance in dogs
Has been given therapeutically intrathecally in people and dogs

Toxic dose, Toxicokinetics, Mechanism of toxicity

Toxic dose:

Currently no established toxic doses in dogs and cats; LD_{50} in dogs and cats unknown
A dose of 0.7 mg/kg has been reported to cause signs in a dog; likewise a dose of 1.3 mg/kg
Death reported in dogs with doses as low as 8-16 mg/kg; one retrospective case series reported death in a dog following exposure to 2.3 mg/kg but the patient did not receive medical attention until several hours after ingestion (and a dog with 61 mg/kg exposure in the same series survived with appropriate management)

Some references cite extra-label *therapeutic* doses for urinary retention (baclofen may decrease urethral resistance) in dogs of:

- 1-2 mg/kg per os every 8 hours
- 5-10 mg total dose per os every 8 hours

As can be see, it has a narrow margin of safety
Not recommended in cats

Given the wide range of toxic doses in reported cases, all ingestions of baclofen should be considered clinically important at this time.

Toxicokinetics:

Rapid and substantial absorption from gastrointestinal tract (peak plasma concentration in people in 2-3 hours) – absorption prolonged with overdose
Wide interpatient variation in people
Wide volume of distribution

- Low protein binding
- Moderately lipophilic

Only small percentage crosses blood-brain barrier (BBB) at therapeutic doses so spinal effects predominate and CNS effects should be absent or minimal
With increasing doses, CNS depression and sedation become more marked as it can cross the blood-brain barrier

Primarily renal elimination of unchanged drug (70-85%) – forced diuresis may aid elimination
≤ 15 % of dosage undergoes hepatic metabolism – biliary excretion

Mean elimination half-life in people 2.5-4 hours

Therapeutic doses undergo first order kinetics (rate of elimination depends on concentration)
Toxic doses undergo zero order elimination extending plasma half-life to as much as 34 hours (rate of elimination independent of concentration – because renal tubular transport and hepatic metabolism become saturated)

- Clinical signs of intoxication can continue long after serum concentration normalises because of slow clearance from CNS

Mechanism(s) of toxicity:

Synthetic y-aminobutyric acid (GABA) analogue (chief inhibitory neurotransmitter in CNS)
Exact mechanism of action unknown:

- Acts predominantly at spinal cord level
    - Binds to pre-synaptic $GABA_B$ receptors inhibiting mono- and polysynaptic afferent reflexes by preventing the release of excitatory neurotransmitters – this reduces skeletal muscle spasm caused by upper motor neuron lesions
        - Further stimulation of GABA receptors results in hyperpolarisation and increased inhibitory tone
    - May also have a post-synaptic effect
    - Some effects may not be related to GABA-like structure
- Also works at supraspinal sites that may contribute to clinical effects; e.g. cerebral cortex effect may explain seizure activity
- Additional mechanisms of action may occur with intrathecal administration

Clinical signs

Onset may be very quick (e.g. 15 minutes) or delayed for several hours, often within 1-2 hours
Most common signs are

- CNS depression
- Vomiting
- Ataxia
- Vocalisation
- Coma
- Drowsiness or lethargy
- Hypersalivation
- Agitation

Also wide range of other signs reported including: hypothermia, bradycardia, muscle twitching/tremors, miosis (also mydriasis), disorientation, weakness, recumbency, hypotonia, hypotension, diarrhoea

Although relatively uncommon, most serious signs are:

- **Respiratory depression**: secondary to flaccid paralysis of diaphragm and intercostal muscles
- **Seizures**: may be due to reduced GABA release from pre-synaptic neurons resulting in excessive post-synaptic firing

Duration of signs varies from several hours to several days.

Agitation may also occur as patient undergoes drug withdrawal.

Emergency database

No specific indications in terms of clinical pathology testing; tests may be unremarkable or show abnormalities
Minimum emergency database (PCV/TS, glucose, urea nitrogen) is recommended early on – especially to check glucose in a patient with neurological signs
Pulse oximetry, end-tidal carbon dioxide monitoring and blood gas analysis as indicated according to respiratory status: hypoventilation? Secondary hypoxaemia?
Subsequently routine monitoring, including of electrolytes, is sensible

Plasma chemistry and urinalysis abnormalities reported in dogs and cats include the following; the significance of some findings remains unclear, others are explainable for example by secondary effects of baclofen intoxication:

- Hypokalaemia
- Hypophosphataemia
- Mild-to-severe increases in creatine kinase, AST
- Mild increases in ALP, ALT
- Pigmenturia: both haematuria and myoglobinuria reported

Haematology may be unremarkable or consistent with stress leukogram (thrombocytopenia also been reported)

If facilities can be accessed, it is possible to measure baclofen in serum or urine; in theory this should be zero in a non-intoxicated patient and any positive level may be considered consistent with poisoning (unless patient is receiving therapeutic baclofen).

- Measuring baclofen will confirm the diagnosis but levels are unlikely to be available during the time course of the patient's management; moreover levels do no impact on management choices per se as treatment is determined according to the needs of each individual patient based on clinical status.

Monitor arterial blood pressure – both hypo- and hypertension reported

Case management

Many patients become symptomatic but clinical presentations vary; individualised therapy necessary but err on the cautious side by treating early and aggressively; hospitalisation is often needed
No antidote

Standard gastrointestinal decontamination if within appropriate timeframe; single dose activated charcoal (no enterohepatic circulation so multidose protocol likely to have limited efficacy)
Supportive care, close monitoring of vital parameters, appropriate nursing
Fluid therapy to support perfusion and hydration but also for diuresis: baclofen has low protein binding and significant urinary excretion so forced diuresis should promote elimination

- May also help mitigate nephrotoxicity from myoglobinuria if present due to tremors or seizures

Atropine for bradycardia/bradydysrhythmias
Anti-hypertensive agents may be needed
Mechanical ventilation may be needed for severe respiratory depression – availability?

Various GABA antagonists and other agents have been evaluated (mainly experimentally) for efficacy against baclofen toxicity (e.g. phaclofen, delta-aminovaleric acid, naloxone, Flumazenil) but none shown to be reliably effective as yet.

Intrathecally effective 'antagonists' may not work orally, e.g. physostigmine – although even its efficacy via the intrathecal route is debated.

Diazepam and other benzodiazepines (GABA agonist) have been used to treat baclofen-induced excitation/tremors/seizures but potential risk of worsening sedation and respiratory depression as the two agents apparently act at different GABA receptors. Barbiturates and propofol also bind to GABA receptors and the same concerns may apply. Ultimately, significant neuromuscular signs need to be controlled if present and this must take precedent over theoretical concerns regarding receptor-binding interactions. Using the lowest effective doses of therapeutic drugs is however recommended.

Cyproheptadine (serotonin antagonist, 1.1 mg/kg per os or rectally) has been suggested to potentially help reduce vocalisation/disorientation – mechanism of action and efficacy in baclofen poisoning remains unclear.

Judicious use of opioids, acepromazine, microdose medetomidine may have to be considered in patients with significant agitation/anxiety

As baclofen is moderately lipophilic, there is likely a role for the use of intravenous lipid emulsion in treating acute toxicity. Some reports available of positive response to ILE therapy – increased patient awareness and activity. Use is recommended in moderate-to-severe cases.

Haemodialysis has also been used as an adjunctive therapy to shorten the elimination half-life (baclofen's low protein binding may make it dialyzable, although its moderate lipophilicity may increase its tissue volume of distribution making it less dialyzable)

Prognosis

A wide range of doses has been reported to cause a wide spectrum of clinical signs in dogs and cats, typically including CNS signs. Severity of signs may relate to degree of exposure (i.e. some dose-dependent aspect) but outcome is more dependent on the delay in presentation for treatment and whether or not necessary supportive and intensive care can be provided – both in terms of access to facilities and affordability. The prognosis is generally good including in patients requiring mechanical ventilation (assuming it can be provided!).

Signs usually resolve fully over several days and no residual CNS effects expected (unless secondary to severe seizuring or hypoxia from respiratory depression). Prognosis more guarded with seizures.