Rodenticide intoxication is a common presenting complaint for cats and dogs in the emergency setting. The rodenticides can be classified as either first-generation anticoagulants (warfarin, pindone, chlorophacinone, diphacinone), second-generation anticoagulants (brodifacoum, bromadiolone, difenacoum, and difethialone), and non-anticoagulants (bromethalin, cholecalciferol, and zinc phosphide). The color of the bait alone is not helpful in differentiating amongst the different types. The most commonly available formulations include bars and place packs. Identification of the compound based on the information from the client is imperative to set out a treatment plan and potential hospitalization.

In 2008 the Environmental Protection Agency released their final ruling on the mitigation measures of rodenticides and all products had to be compliant by 2011. This was to reduce the exposure of over 14,000 children annually and non-target wildlife. Some of the changes included 1) the removal of loose bait products (pellets and meal) from commercial products; 2) sale and distribution limits on second-generation rodenticides; 3) rodenticides had to be sold in pre-packaged baited stations or in block formulation (<1 pound); and 4) decrease the availability of second generation rodenticides for residential use. With these new guidelines it is expected that more non-anticoagulant products become more widely used by the general population which might increase the exposure to the small animal population.

Anticoagulant rodenticides

Sweet clover poisoning in cattle led to the discovery of dicouarol which caused internal bleeding in the cattle that ingested, which led to the discovery of anti-coagulant rodenticides. The first commercially available rodenticide was Warfarin which was named after Wisconsin Alumni Research Foundation (WARF) in the 1940s along with other first generation anti-coagulant rodenticides. The first generation anti-coagulants have a shorter half-life and require higher concentrations over several days to deliver its toxic dose. After its wide availability rodents developed resistance to these rodenticides, and thus the second generation were developed. These had a much longer half-life and require smaller doses to develop toxicity.

The anti-coagulant rodenticides affect the Vitamin K dependent clotting factors (II, VII, IX, X). In health Vitamin K \(_1\) is converted to Vitamin K \(_1\) epoxide during normal production of the clotting factors. Vitamin K \(_1\) epoxide is recycled back into its active form by Vitamin K \(_1\) epoxide reductase. This enzyme is what is inhibited by the anti-coagulant rodenticides which leads to a decrease in active Vitamin K \(_1\) and stops the production of these clotting factors. It is not until days 3 to 5 when the factors are depleted that patient develop clinical signs of bleeding.
Clinical signs in patient with anti-coagulant rodenticide are secondary to hemorrhage. Cavitary bleeding is most commonly seen which abdominal, pleural, and pericardial bleeding being common. There is can also be gastrointestinal bleeding, joints, and CNS. Coughing, dyspnea, hemoptysis, hematemesis, melena, pallor, weakness, decreased heart or lung sounds, hyphema, and hematomas can be seen. Acute CNS such as seizures, paresis, paralysis and death could occur. Ocular signs including subconjunctival hemorrhage, exophthalmos, extraorbital pain, and hyphema have been reported to occur without the presence of systemic signs in dogs with anti-coagulant rodenticide ingestion.

Diagnosis is commonly based on recent history and evaluation of clotting times. Factor VII has a short half-life and thus will be depleted within 36 to 72 hours leading to an elevation of PT. After 3 to 5 days the other factors are depleted causing elevations in PTT and ACT. PIVKA (precursors of the vitamin K–dependent clotting factors) will also become increased within 36 to 72 hours. Other laboratory findings might include anemia, thrombocytopenia, and hypoproteinemia.

Treatments should be based on whether patient is clinical and the time of exposure. LD50 for warfarin is 20-50 mg/kg, while Brodifacoum can be as low as 0.2-0.4 mg/kg. In patients where ingestion occurred <1 hour prior to presentation emesis should be induced. Apomorphine can be used in a ocular formulation (6mg tablets) and injectable (0.02-0.04 mg/kg IV). Hydrogen peroxide can be used at (1ml/pound) but side effects include gastric mucosa sloughing and aspiration pneumonia. For this reason it should not be administered by owners. After emesis or if patient had ingested the rodenticide > 1 hour activated charcoal should be given without sorbitol. A single dose (2 – 5 g/kg) can be given. Patients should have PT/PTT checked 36-72 hours after exposure and if elevated Vitamin K1 should be started at 1.5-2.5 mg/kg PO q12h x 4 weeks with food (although high fat meals have been recommended). In clinical patients initial stabilization including oxygen and fluid therapy should be started. Once confirmation of rodenticide ingestion has occurred replacing the clotting factors is of upmost importance. The use of fresh frozen plasma or frozen plasma at 10-20ml/kg over 2-4 hours should be started. Vitamin K1 should be started orally as soon as the patient is able to eat. Alternatively Vitamin K1 could be given subcutaneous however there is a risk of developing a hematoma. Intravenous Vitamin K1 should be avoided due to risks of potential anaphylaxis.

Bromethalin

Bromethalin intoxication has become prevalent in veterinary medicine since the recent increase of its use in rodenticide products. It is commonly available in 1 oz blocks with a concentration of 0.01% (2.84 mg/block). It is readily absorbed from the gastrointestinal tract (4 hours in rats) and it is metabolized in the liver to desmethylbromethalin. It has a high volume of distribution and is commonly found in high concentrations within the brain and fat tissue. Excretion occurs slowly through bile and there is evidence of enterohepatic recirculation. Bromethalin uncouples oxidative phosphorylation leading to ATP depletion decreasing energy available for Na/K pumps. This leads to decreased brain cellular function, electrolyte imbalance, and fluid shift into the myelinated areas within the brain and spinal cord leading to increased intracranial pressure.

The lethal dose 50% (LD50) in dogs is reported to be 2.38-5.6 mg/kg, with signs reported with doses as low at 0.95mg/kg. Cats appear to be more sensitive with an LD50 0.4 -0.71 mg/kg.
Exposure and signs are dependent on the dose ingested. The convulsant syndrome is seen in patients that ingest > LD₅₀. Clinical signs occur between 2-14 hours after exposure. Clinical signs include hyperesthesia, hyperexcitability, tremors, seizures, circling, vocalization, mild to severe CNS depression, hyperthermia, and death. Treatment in these patients include supportive care including hypertonic saline, benzodiazepines, mannitol, and barbiturates. Recently the use of intravenous lipid emulsion (ILE) has been postulated due to the lipophilic nature of bromethalin. A recent evaluation of a single case that did not have clinical signs at presentation showed a 75% decrease in desmethylbromethalin with hours of the ILE being given. The paralytic syndrome can be seen in patients that have ingested less than the LD₅₀ and clinical signs developed within 1 to 7 days. These can include ataxia, paresis, paralysis, CNS depression, muscle tremors, nystagmus, anisocoria, dysphoria, dysuria, seizures, and death. In cats abdominal distension and ileus has been described. Supportive care is the standard of care. In patients with a recent exposure (<1hr) emesis and activated charcoal should be used. In patients with a recent exposure (>1hr) but no clinical signs single dose or multiple doses (4 doses 6 hours apart) of activated charcoal should be used.

**Cholecalciferol**

Cholecalciferol (Vitamin D₃) is commonly obtained by mammals through their diet or by dermal ultraviolet exposure. Cholecalciferol is metabolized in the liver to calcifediol (25-hydroxycholecalciferol) which then is metabolized by the kidney to calcitriol (1,25-dihydroxycholecalciferol). Calcitriol is the most active metabolite which has a strong negative feedback mechanism which halts its production. Calcifediol has a poor feedback mechanism leading to increased levels in the body with increased levels of cholecalciferol. Calcifediol leads to an increase in calcium and phosphorus within the body leading to clinical signs. This is by increased calcium absorption from the gastrointestinal tract, increased renal tubular reabsorption and increased calcium removal from bone to plasma. Cholecalciferol is highly lipid soluble and therefore is slowly released from the body. Due to the long half-life of calcifediol (15 days) most patients need to be treated for long periods of time.

Clinical signs from cholecalciferol can be seen at a dose of 0.5mg/kg in dogs. Each 1 oz block with a concentration of 0.075% contains 21 mg of cholecalciferol. This means that ½ a block could lead to clinical signs in a 22kg dog. Initial clinical signs can be seen within 12-36 hours causing polyuria, polydipsia, anorexia, depression, and vomiting. Muscle weakness will develop within 48 hours. Prolonged elevation of calcium and phosphorus levels leads to tissue mineralization which can lead to acute kidney injury. Long term prognosis depends on the degree of renal mineralization. In severe cases chronic kidney disease should be expected if patient survives the acute intoxication.

Diagnosis is frequently made by the owner noticing the rodenticide in the stool or noting the ingestion of the rodenticide. Laboratory test may show increased in phosphorus, calcium (ionized and total), and azotemia. Isosthenuria is commonly seen and mineralization may be seen in radiographs. Testing for calcifediol can be performed. Treatment should be based on the time of exposure. If ingestion occurred less than 1 hour prior to presentation then emesis and activate charcoal should be performed. If patient is having clinical signs gastrointestinal decontamination will not be helpful. Instead management of azotemia with NaCl 0.9% for diuresis, gastric protectants, and supportive care should be started. After patients
have been rehydrated the administration of furosemide at 0.5-1.0 mg/kg to promote diuresis and calcium wasting, by inhibiting calcium reuptake. In patients with severe clinical signs or persistent hypercalcaemia pamidronate, a biphosphonate, which inhibits bone resorption. A dose of 1.5-2.0 mg/kg IV infusion diluted in 150-250 mls of NaCl 0.9% over 4 to 6 hours. Due to its long half-life (29 days) fluid diuresis may be required for over 7 days. The fluid of choice is NaCl 0.9% given at 4 – 6 mls/kg/hr (twice maintenance) which prevent volume depletion and limits renal calcium reuptake. After resolution of azotemia furosemide and prednisone may be started and tapered at home for 14 days to continue to promote diuresis.2 Prednisone and prednisolone will decrease bone resorption, increased calcium excretion, and decreases intestinal calcium absorption.

Rodenticide intoxication despite of formulation has a favorable prognosis if patients are brought in to the emergency department shortly after ingestion and prior to clinical sign development. Gastrointestinal decontamination is the preferred treatment for all asymptomatic patients. Induction of emesis should only be ensued if a recent (<1 hour) exposure is suspected. The delayed administration of activated charcoal could be detrimental. If the time of exposure is not known administration of activated charcoal (single or multiple doses) should be performed. Symptomatic patients will require aggressive therapy and prognosis is dependent on the clinical signs observed for each rodenticide.

References:

5. Papich M. Sanders Handbook of Veterinary Drugs Small and Large Animal. 3251 Riverport Lane St. Louis, Missouri 63043, Saunders, an imprint of Elsevier Inc; 2011.