Treating Tough Toxins

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Cholecalciferol

Cholecalciferol is a Vitamin D3 analog. It can be found in rodenticides, oral vitamins and dermal preparations for psoriasis (Dovonex®). Cholecalciferol alters calcium metabolism in the body, increasing intestinal absorption and renal tubular reabsorption of calcium and stimulating bone resorption. Clinical signs of intoxication usually develop within 12-36 hours. Early signs include lethargy, weakness, anorexia, polydipsia, polyuria, and vomiting, often with blood. Biochemical alterations include hyperphosphatemia within 12 hours and hypercalcemia within 24 hours of exposure and azotemia (both renal and pre-renal). The elevated calcium levels result in calcification of many tissues, notable renal tubules and walls of blood vessels. The elevated calcium also has a direct effect on kidney function, sometimes causing acute renal failure even without mineralizations.

Diagnosis of toxicosis is based on history of exposure, clinical signs, serum chemistries and urinalysis. Run baseline chemistries as soon as possible after a known exposure. Pursue GI decontamination if within several hours of ingestion, or if there is evidence of ingestion (chewed box) at unknown time but a still asymptomatic animal. Decontamination consists of multiple doses of activated charcoal and possibly cholestyramine. Cholestyramine is an anion exchange resin available by prescription only. It is used as an adjunctive therapy for the lowering of serum cholesterol in patients with primary hypercholesterolemia who have not responded to diet or other measures alone. Cholestyramine is also indicated for use in the relief of pruritus associated with partial biliary obstruction. It has also been used to aid in the treatment of toxicoses in humans (amiodarone, digitoxin, iopanoic acid, kepone, chlordane, leflunomide, methotrexate, mycophenolic acid, piroxicam, tenoxicam, phenprocoumon, pfiesteria toxin, thyroid, Vitamin D, warfarin, blue-green algae, indomethacin).

Cholestyramine binds with bile acids in the intestine, preventing their reabsorption and producing an insoluble complex, which is excreted in the feces. Cholestyramine has been shown to decrease the toxicity of indomethacin in the dog. Animals are dosed at 0.3 – 1 g/kg TID for several days (depends on toxin ingested). The powder should be given before feeding if possible or mixed with canned food. Cholestyramine is not absorbed out of the digestive tract, so it has no systemic effects other than possible constipation. If giving with activated charcoal, alternate q 4 hours.

Treatment for cholecalciferol is aimed at lowering the serum calcium and phosphorus levels if elevated, preventing a rise in these values if still normal, and stopping further calcium mobilization from the bones. IV normal saline at twice maintenance, prednisone and furosemide all enhance calciuria. Monitor serum calcium, phosphorus, BUN and creatinine daily to judge effectiveness of therapy. If calcium levels are rising despite calciuresis, best choice is pamidronate (Aredia™). Unlike salmon calcitonin, it needs to be given only once, with a repeat dose possibly at about 5-7 days. It acts at the level of the osteoclast and is deposited in the bone itself. Dose is 60-90 mg (about 1.3 mg/kg) mixed in 500-700 ml saline and given slowly over 2-4 hours. The advantage is that it works quickly in a majority of dogs and cats. Once the pamidronate has been administered, it is important to taper the initial treatments (prednisone, furosemide) and decrease the rate of fluid administration. Continue to monitor calcium, phosphorus, and kidney values during this time. End of therapy will be marked by a return to normal of kidney values and the decrease of calcium and phosphorus levels.

Phenylpropanolamine

Phenylpropanolamine (PPA, Proin®) is a sympathomimetic agent. PPA has been withdrawn from the human market due to an association with increased stroke risk, but it is still used in veterinary medicine for controlling urinary incontinence in dogs. Signs can be seen at therapeutic doses in some dogs and serious signs appear at doses above 20 mg/kg. Signs include tachycardia, hypertension, panting, excitement/hyperesthesia, piloerection, tremors, and seizures. Reflex bradycardia may occur secondary to the hypertension; therefore, dogs may present either depressed, bradycardic and hypertensive OR agitated, tachycardic and hypertensive. Signs normally start within 30-90 minutes and may continue up to 48 hours, depending on dose.

Emesis may be induced if the ingestion was witnessed and within 10-15 minutes. Activated charcoal should be given if possible. Heart rate and blood pressure should be closely monitored. Nitroprusside or other pressor agents can be used to manage hypertension. Managing the blood pressure often results in correction of the reflex bradycardia. Atropine is contraindicated in the management of bradycardia as it will worsen the hypertension. Beta blockers should NOT be used on bradycardic animals as they may precipitate a hypertensive crisis. Phenothiazines (acepromazine or chlorpromazine) may be used to control hyperesthesia and excitement. Animals should be put on IV fluids to promote excretion, protect renal function and help with thermoregulation. As with other stimulants, cyproheptadine may be given if signs of serotonin syndrome develop.

Baclofen

Baclofen is a centrally acting skeletal muscle relaxant that mimics γ-aminobutyric acid (GABA) within the spinal cord and causes a flaccid paralysis of skeletal muscles. At oral therapeutic levels, baclofen has virtually no CNS effects due to its poor ability to cross the blood brain barrier, but in overdose situations, CNS effects are common. The most common clinical signs of toxicosis are vomiting, ataxia and vocalization/disorientation, but the most life threatening signs are dyspnea, respiratory arrest and seizures. Dyspnea and respiratory arrest are secondary to paralysis of the diaphragm and intercostal muscles.

The onset of clinical signs varies in dogs with signs occurring anywhere from 15 minutes to 7 hours post exposure (average of 1.9 hr). Duration of clinical signs vary from several hours to several days. Signs can continue long after serum baclofen levels have returned to normal due to the slow clearance from the CNS. Dog doses as low as 1.3 mg/kg can cause vomiting, depression and vocalizing. There are no established lethal doses in animals, but per the APCC data base, deaths in dogs have occurred at doses as low as 8 mg/kg.

Due to the rapid onset of clinical signs, emesis should be considered in only the asymptomatic, recently exposed patient. Gastric lavage may be considered with large ingestions, but care must be taken to ensure that anesthesia does not compound CNS depression. Short acting induction agents such as propofol followed by inhalent anesthesia with a protected airway is preferred. All asymptomatic cases should receive activated charcoal with a cathartic. Avoid magnesium-based cathartics (Epsom salts), as they may worsen CNS depression. Exposed animals should be monitored for 12 hours for development of clinical signs.

Ventilatory support is a prime concern and endotracheal intubation and positive pressure mechanical ventilatory support may be needed for an extended time in severe cases. Diazepam is the drug of choice for centrally acting skeletal muscle relaxant induced seizures. Propofol or isoflurane may be considered in cases that are refractory to diazepam. Long acting barbiturates or other agents that produce profound or prolonged CNS depression should be used with care. Cyproheptadine (1.1 mg/kg PO or rectally) has been used successfully to reduce the vocalization/disorientation seen in some animals. Fluid diuresis is used to enhance elimination and maintain blood pressure. Intralipids have been used successfully in early intoxications. The use of CNS respiratory stimulants are of questionable value and experimental studies have failed to consistently produce positive outcomes when flumazenil was used and have potential to cause serious adverse effects (seizures). Prognosis is variable, and can depend on the availability of ventilatory support for depressed patients. Prognosis is more guarded if seizures develop.

Calcium channel blockers (CCB)

Calcium channel blockers (verapamil, diltiazem, nifedipine, etc.) slow the activity of the SA pacemaker as well as conduction through the AV node. They also cause frequency-dependent channel blockade in the AV node so that it is effective in slowing supraventricular arrhythmias. Calcium channel blockers reduce total peripheral resistance, blood pressure, and cardiac afterload. They can also cause negative inotropic effects, but this is rarely of clinical significance.

Calcium channel blockers have a low margin of safety, causing hypotension and dysrhythmias. Bradycardia and AV nodal depression are the most common dysrhythmias, although others are possible. Hyperglycemia, hyperkalemia, hypokalemia, and hypocalcemia are possible. Due to a rapid onset of signs, the induction of emesis may not be appropriate. Standard decontamination practices should be performed in cases of significant exposure. Any dose exceeding the therapeutic dose should be monitored for cardiovascular signs. Fluid replacement and calcium chloride administration may help correct blood pressure and conduction abnormalities. Calcium gluconate (1 ml/10 kg of 10% solution) may be less effective than calcium chloride but can be used. Monitor for hypercalcemia if calcium is supplemented. Atropine and isoproterenol may be used for bradyarrhythmias and may be more effective following calcium administration. If hypotension persists, norepinephrine, neosynephrine, dopamine, dobutamine, or amrinone are recommended. Insulin and dextrose infusions in a canine model improved survival following verapamil overdose. The newest treatment is intralipids. Prognosis is dependent on dosage and response to therapy. Noncardiogenic pulmonary edema has been reported in cases of massive overdose.

Digoxin

Digoxin is a digitalis glycoside that can be found in elixers (0.05 and 0. 15 mg/ml), tablets (0. 125, 0.25 and 0.5 mg) and capsules (0.05, 0.1 and 0.2 mg). Digitalis-like compounds (cardiac glycosides) are also found in several plants: oleander (Nerium oleander), foxglove (Digitalis purpurea), Kalanchoe sp. and lily-of-the-Valley (Convallaria majalis). These compounds inhibit the myocardial cell membrane Na-K ATPase pump. This inhibition results in increased intracellular sodium concentrations. The sodium must exit by exchanging with extracellular calcium. The sarcoplasmic reticulum binds the excess calcium and uses it to increase contractility. Digitalis is used in the treatment of congestive heart failure, atrial fibrillation or flutter and supraventricular tachycardias.

Absorption following oral administration occurs in the small intestine and is variable dependent on the oral dosage form used. Food may delay, but does not alter, the extent of absorption. Peak cardiac effects are seen in 6-8 hours. Digoxin is distributed widely throughout the body with highest levels found in kidneys, heart, intestine, stomach, liver and skeletal muscle. The half life of digoxin is 14.4 - 56 hours in the dog and 23.8 – 42.8 hours in the cat.

Adverse effects of digitalis glycosides are usually associated with high or toxic serum levels and are categorized into cardiac and extracardiac signs and symptoms. Cardiac effects may include almost every type of arrhythmia described. The more common arrhythmias or ECG changes seen include: complete or incomplete heart block, bigeminy, ST segment changes, paroxysmal ventricular or atrial tachycardias with block, and multifocal PVCs. Extracardiac effects most commonly seen in veterinary medicine include mild GI upset, anorexia, weight loss, depression and diarrhea. Hyperkalemia and hyponatremia are seen with overdosage.

In dogs the acute toxic dose after IV administration has been reported to be 0.177 mg/kg. The minimum lethal dose of cardiac glycosides are not well established, but 0.33 mg/kg orally in a dog was lethal. Drug levels may be available from a human hospital on a "stat" basis. Cats are relatively sensitive to digoxin while dogs tend to be more tolerant of high serum levels. Therapeutic range for the dog is 0.9 - 3.0 ng/ml (<6.0 ng/ml is moderately toxic; >6.0 ng/ml is highly toxic). Therapeutic drug levels in the cat are 0.9 - 2.0 ng/ml.

Emesis can be induced with recent ingestion in an asymptomatic animal. Activated charcoal decreases digoxin absorption up to 96%. In the symptomatic patient supportive and symptomatic therapy should be implemented. IV fluids should be started at maintenance rate, but do not use calcium-containing fluids like Ringer's or LRS. Forced diuresis does not accelerate the elimination of cardiac glycosides and may worsen electrolyte imbalances. Serum electrolytes, arterial blood gases, and continuous ECG monitoring should be instituted. In severe intoxication, monitor serum potassium hourly.

The use of specific antiarrhythmic agents in treating life-threatening digitalis-induced arrhythmias may be necessary. **Phenytoin and lidocaine** are the drugs of choice for tachyarrhythmias because they reduce automaticity, disrupt re-entrant pathways and reduce sympathetic tone. **Propranolol** is the next choice as it blocks sympathetic nerve activity. Atropine may be used to treat sinus bradycardia, SA arrest, or 2nd or 3rd degree AV block. Digibind® (Burroughs Wellcome Co., Research Park Triangle, NC) is a specific antagonist to digoxin. It is an immune Fab produced from specific digoxin antibodies from sheep and will bind directly to the drug, inactivating it. It is expensive however and several vials may be needed for treatment. Prognosis is guarded with large ingestions especially in patients with underlying disease and risk factors.

5-Fluorouracil

5-Fluorouracil (5-FU) is in the antimetabolite class of antineoplastic agents. The topical creams and solutions (Efudex, Fluoroplex, Adrucil) are extremely toxic if ingested. 5-FU destroys rapidly dividing cells, causing severe vomiting and GI irritation. It is likely converted to fluorocitrate affecting the Krebs cycle and causing seizures similar to fluoroacetate. If given enough time (5-20 days) and if the animal survives, it could destroy bone marrow stem cells resulting in leukopenia which can progress to a pancytopenia. This may be due to the 5-FU metabolite, FdUMP, not readily diffusing across cell membranes as 5-FU does, leading to delayed clearance from the bone marrow.

The onset of clinical signs usually occurs within 0.5 to 5 hours following ingestion. 5-FU rapidly distributes to the total body water and it is absorbed by all cells. In dogs that survived, signs lasted from 18 hours to 14 days. The minimum lethal oral dose for the dog is 20 mg/kg, but signs of toxicity are seen as low as 8.6 mg/kg. Often signs begin with vomiting (with or without blood) and progress to tremors and seizures within a few hours. The vomiting isn't always seen before seizures, nor are seizures seen in every case. Seizures may require care for more than 24 hours.

Emesis, activated charcoal and cathartic can be started if the animal is asymptomatic and the ingestion was recent (less than 1 hour). Seizures and tremors are rarely controlled with diazepam. Pentobarbital, phenobarbital, gas anesthetics (isoflurane), and propofol have been used successfully. GI protectants and antiemetics should be started. IV fluids, thermoregulation, antibiotics, and pain control are very important parts of the therapy. If animals live through the severe vomiting and seizures, WBC's could start to decline in 5-20 days. Filgrastim (Neupogen) may be given for neutropenia (5-6 mg/kg SQ). Prognosis is guarded to poor once signs occur. Sixty-four percent of dogs ingesting 5-FU die or are euthanized.

Flucytosine is an antifungal agent that must be converted to 5-FU by cytosine deaminase to have cytotoxic effects. Mammalian cells lack cytosine deaminase, however, if taken orally, microbes in the GI tract will convert flucytosine to 5-FU and could result in toxicosis.

5-HTP

5-hydroxytryptophan (5-HTP, griffonia seed extract) is a precursor of serotonin. 5-HTP is available over-the-counter and is used to treat a variety of disorders including obesity, depression, anxiety, insomnia, PMS, and compulsive gambling. Overdoses of 5 HTP induce "serotonin syndrome" due to overstimulation of serotonin receptors in nervous system, gastrointestinal tract, cardiovascular and respiratory systems.

Serotonin syndrome was originally classified in humans and defined as a constellation of symptoms that included at least three of the following: myoclonus, mental aberration (dementia, disorientation, etc.), agitation, hyperreflexia, tremors, diarrhea, ataxia and hyperthermia. This “classic” definition of serotonin syndrome has recently become controversial although a majority of cases of serotonin syndrome in humans and animals will fulfill these criteria.

In addition to the CNS and GI tract (where serotonin is a modulator of gastrointestinal smooth muscle contractility), respiratory and cardiovascular function may be altered in serotonin syndrome due to the importance of serotonin in maintaining vascular tone, stimulating bronchial smooth muscle, and stimulating cardiac stroke rate and volume. In general, these effects are not as clinically relevant as the GI and CNS signs. Alteration in platelet function or coagulation, both areas in which serotonin plays important role, has not been described in cases of serotonin syndrome in humans or animals.

In dogs the most common clinical signs include: vomiting, diarrhea, seizures, hyperthermia, hyperesthesia, depression, mydriasis, vocalization, death, blindness, hypersalivation, dyspnea, ataxia/paresis, disorientation, hyperreflexia, and coma. Signs are similar, but vary in severity, whether 5-HTP or other serotonergic drugs such as SSRIs or MAOIs are ingested.

Treatment of serotonin syndrome is largely symptomatic and supportive. Inducing vomiting is not recommended if clinical signs are present because of the increased risk of aspiration. Seizures and agitation generally respond to diazepam or phenothiazines (the drug of choice in humans), and barbiturates can be used in refractory cases. Because hyperthermia is a significant concern, cooling measures should be instituted. Diuresis does not enhance excretion, but intravenous fluids should be administered to support the cardiovascular system, aid in thermoregulation, and maintain renal blood flow. The use of cyproheptadine, a nonselective serotonin antagonist, has shown to be a helpful adjunct in managing serotonin syndrome in animals. Cyproheptadine may be administered at a dose of 1.1 mg/kg PO (dogs) or 2-4 mg PO (cats). In cases where the oral route is not feasible (e.g. severe vomiting), cyproheptadine may be crushed and mixed with saline to be instilled rectally. Doses of cyproheptadine may be repeated every 4-6 hours as needed until signs have resolved. Propranolol also has some serotonin blocking effect, and may be of benefit if animals are tachycardic. Administration of activated charcoal is important, but only once the animal has been reasonably stabilized. Metabolic acidosis may occur and can be corrected with sodium bicarbonate as indicated by blood gas analysis. Symptomatic care to control vomiting, abdominal pain, or other signs can be instituted as needed.