Cholecalciferol Poisoning
by

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Cholecalciferol (vitamin D_3) is found commercially in rodenticides and vitamin supplements. One IU of vitamin D_3 is equivalent to 0.025 µg of cholecalciferol.[1] *Table 1* lists some common products that contain cholecalciferol.

Cholecalciferol is rapidly absorbed after ingestion. The parent compound and metabolites are fat soluble and, thus, are stored in adipose tissue. Enterohepatic recirculation of cholecalciferol and its metabolites occurs.[2] With normal dietary intake, cholecalciferol is converted to 25-hydroxycholecalciferol (calcifediol) by 25-hydroxylase in the liver. There is limited negative feedback of calcifediol on the activity of hepatic 25-hydroxylase, and its activity is not influenced by plasma calcium and phosphorus concentrations.[3] Calcifediol becomes metabolically activated to 1,25-dihydroxycholecalciferol (calcitriol) in the kidneys by 1-α-hydroxylase. The rate of renal 1-α-hydroxylase activation depends on plasma concentrations of parathyroid hormone, calcium, phosphorus, and calcitriol.[3]

After a massive cholecalciferol intake (*i.e.* after ingesting a cholecalciferol-containing rodenticide), excess calcifediol is produced in the liver. Calcitriol is initially produced in the kidneys, but once a set plasma concentration of calcitriol is reached, it exerts negative feedback on renal 1-α-hydroxylase, and no more calcitriol is produced.[3] However, because of the limited negative feedback on hepatic 25-hydroxylase, calcifediol concentrations continue to increase, and the plasma concentrations of calcifediol become high enough to exert metabolic effects.[3]

Because of their high lipid solubility, cholecalciferol and its metabolites are eliminated slowly from the body. Cholecalciferol has a plasma half-life of 19 to 25 hours and a terminal half-life (the time needed for the amount of a compound present in all body stores to decrease by half) of weeks to months.[2] Calcifediol has an experimental elimination half-life of 19 days.[2] Metabolites are eliminated primarily (96%) through the bile and feces.[3]

Mechanism of action
The metabolic activity of cholecalciferol and its metabolites is variable. Calcitriol is the most metabolically active and binds to the vitamin D receptors 500 times greater than calcifediol does and 1,000 times greater than cholecalciferol does.[3]

The active metabolites increase plasma calcium and phosphorus concentrations through two primary mechanisms. First, they increase the amount of intestinal calcium-binding protein (calbindin). The amount of calcium absorbed is directly related to the amount of calbindin in the enterocytes.[4] Thus, more calcium is absorbed from the intestines when calbindin is increased. Second, cholecalciferol metabolites stimulate calcium and phosphorus transfer from bone to plasma.[3]

Clinical signs (vomiting, lethargy, muscle weakness) seen within the first 48 hours of cholecalciferol overdose are due to the direct effect of increased plasma calcium concentrations on cells. These cellular effects include altered cell membrane permeability, altered calcium pump activity, decreased cellular energy production, and cellular necrosis.[3] Specific organ effects include acute renal tubular necrosis, gastrointestinal stasis, increased gastric acid secretion, decreased skeletal muscle responsiveness, and decreased neural tissue responsiveness.[3]

With an unregulated increase in plasma calcium and phosphorus concentrations, the plasma calcium X phosphorus product can rise above 60, which will likely cause soft tissue mineralization.[5] Mineralization of the kidneys, gastrointestinal tract, cardiac muscle, skeletal muscle, blood vessels, and ligaments causes structural damage that leads to decreased functional capacity of these tissues and organs. This loss of function contributes to the development of ongoing and end-stage clinical signs as well as long-term signs in animals that survive.[3]

Toxicosis and risk factors

Any animal that ingests cholecalciferol-containing rodenticides has a greater risk of developing toxicosis than does an animal that ingests supplements that contain vitamin D. Clinical signs can be seen at 0.5 mg/kg of cholecalciferol.[6] This corresponds to 6 g (79 pellets or about ½ tbsp) of a typical 0.075% cholecalciferol rat bait ingested by a 20-lb (9-kg) dog.[7] The amount of cholecalciferol in most vitamin supplements is not considered a risk for companion animals, even with massive ingestion. While a pet ingesting large amounts of vitamin supplements may develop a self-limiting gastroenteritis, the signs can be attributed to nonspecific gastrointestinal irritation. Relay toxicosis (i.e. toxicosis in an animal that has ingested a rodent that died of cholecalciferol poisoning) with cholecalciferol baits has not been reported.

Clinical signs

Signs of acute toxicosis develop within 12 to 36 hours after ingestion.[6] They include vomiting and diarrhea (sometimes bloody), anorexia, depression, and possibly polyuria and polydipsia.[8,9] With high doses, fulminant acute renal failure can occur within 24 to 48 hours. Death can result from acute renal failure in severely affected animals. Animals that survive may lose renal or musculoskeletal function and may develop cardiac arrhythmias.[3] Clinical signs and subsequent treatment may last for weeks because of the lipid storage and slow elimination of the cholecalciferol metabolites.

Clinical pathology

In cases of acute toxicosis, there is a moderate rise in the serum phosphorus concentration (up to 11 mg/dl) and a more severe rise in the serum calcium concentration (up to 20 mg/dl).[8-10] The calcium X phosphorus product may easily exceed 130. These changes are seen between 12 and 72 hours after exposure.[8-10] Secondary increases in blood urea nitrogen and creatinine concentrations may also occur in this time frame. Urine specific gravity becomes isosthenuric.

Diagnostic testing

You must rule out other causes of hypercalcemia when a patient has an uncertain history of cholecalciferol exposure. These causes include hypercalcemia when a patient has an uncertain history of cholecalciferol exposure. These causes include hypercalcemia of malignancy (mediated through parathyroid hormone-related peptide), hypoadrenocorticism, chronic renal failure, primary hyperparathyroidism, feline idiopathic hypercalcemia,[11] and ingestion of human prescription skin products containing the vitamin D analogues calcipotriene or tacalcitol.[12,13] (For more information on calcipotriene poisoning, see "Calcipotriene poisoning in dogs," Oct. 2000, p. 770.)

A parathyroid hormone/parathyroid hormone-related peptide/calcifediol assay may help differentiate among the various causes of hypercalcemia (Table 2).[5] This assay should detect overexposure to cholecalciferol products, since calcifediol is elevated during cholecalciferol toxicosis. However, easy and routine assays for calcipotriene, tacalcitol, and calcitriol are lacking, making a definitive diagnosis through chemical identification of these analogues difficult.

If you are submitting samples for a parathyroid hormone/parathyroid hormone-related peptide/calcifediol assay, contact your diagnostic laboratory to confirm test availability. If the assay is unavailable, antemortem serum analysis for parathyroid hormone/calcifediol and antemortem plasma analysis for parathyroid hormone-related peptide can be performed at Michigan State University. Send chilled samples to the Animal Health Diagnostic Laboratory, Endocrine Diagnostic Section, 619 W. Fee Hall B, Michigan State University, East Lansing, MI 48824-1315. For more information call (517) 353-0621, or visit www.ahdl.msu.edu.

Treatment

In cases in which the exposure is recent, an animal is asymptomatic, and there are no underlying contraindications to emesis (*e.g.* underlying cardiac or seizure disorders, the patient is a lagomorph or rodent), induce vomiting. All asymptomatic patients should receive activated charcoal (1 to 2 g/kg mixed with 50 to 200 ml water administered orally; or 240 ml commercial slurry per 25- to 50-lb [11- to 23-kg] animal) given with a cathartic. Many commercial slurries contain sorbitol as a cathartic. If a slurry does not contain a cathartic, ¼ tsp Epsom salts (magnesium sulfate)/10 lb can be added. In cases of large or massive ingestion, repeated doses of activated charcoal at half the initial dose and without a cathartic may be given

at six- to eight-hour intervals for 48 hours. Multiple doses of activated charcoal may help interrupt enterohepatic recirculation of cholecalciferol and its metabolites.

Obtain baseline measurements of serum calcium, phosphorus, blood urea nitrogen, and creatinine concentrations, and monitor these parameters daily for four days. If the values stay normal and the patient remains asymptomatic, no further monitoring or treatment is necessary.[12]

In animals that develop clinical signs or elevations in serum calcium concentrations, initial treatment consists of diuresis with intravenous 0.9% saline solution at two to three times the maintenance rate. Saline is preferred because it contains no calcium, and the sodium ions reduce tubular calcium reabsorption, leading to increased calcium excretion.[3]

Once an animal's hydration status is normal, administer furosemide as a 5 mg/kg intravenous initial bolus and then as a 5-mg/kg/hr constant-rate intravenous infusion[3]; 2 to 4 mg/kg furosemide given orally every eight hours is another option.[14] Furosemide decreases sodium and chloride reabsorption across Henle's loop, resulting in a diminished positive potential across the renal tubule. This diminished potential increases renal calcium excretion.[3] Carefully monitor hydration status, and reduce the amount of furosemide in the constant-rate infusion if dehydration develops.[3] Do not use thiazide diuretics, because they are calcium-sparing.[3]

Administering prednisone at 1 to 2.2 mg/kg every 12 hours orally will decrease serum calcium concentrations by decreasing bone resorption and intestinal calcium absorption and increasing renal calcium excretion.[3]

Phosphate binders (aluminum hydroxide [Amphojel – Wyeth-Ayerst]; 30 to 90 mg/kg/day divided, given orally with meals) and a low-calcium, low-phosphorus diet are recommended to decrease dietary mineral absorption while a patient is being treated and monitored (generally four weeks).[3] Affected animals should avoid sunlight to prevent endogenous cholecalciferol formation. Carefully consider using activated charcoal in symptomatic patients, weighing the risk of aspiration in a vomiting animal against the benefit of activated charcoal.

Continue intravenous saline solution administration until serum calcium concentrations are normal.[12] Furosemide and prednisone can be continued for one or two weeks after you discontinue the intravenous saline solution and then gradually reduced.[3] Monitor calcium concentrations daily for four days after stopping fluids, twice a week for two weeks after that, and then weekly for two weeks.[3]

Severely affected animals, animals whose calcium concentrations do not respond to initial therapy, or animals who relapse after fluid discontinuation may benefit from treatment with a bisphosphonate. The bisphosphonate pamidronate disodium (Aredia – Novartis) has been used successfully in dogs for cholecalciferol toxicosis. Pamidronate (1.3 to 2 mg/kg diluted with saline solution and given intravenously over two hours) reduces serum calcium concentrations.[15] Maintain the animal on therapeutic intravenous saline solution (two to three times the maintenance rate) until the calcium concentrations are normal. Once serum calcium concentrations return to normal, monitor them daily for four days. Pamidronate retreatment five to seven days later may be necessary.

Bisphosphonates lower plasma calcium by inhibiting bone reabsorption of calcium through blocking dissolution of hydroxyapatite and inhibiting osteoclastic bone resorption.[15] While biphosphonates are expensive, they may save a client money in the long run. They lower plasma calcium concentrations in 24 to 48 hours, allowing a patient to be treated on an outpatient basis instead of being hospitalized and receiving intravenous saline solution for two to four weeks.

If a bisphosphonate is not available, salmon calcitonin (4 to 6 IU/kg t.i.d. subcutaneously) may be used to lower serum calcium.[3] Salmon calcitonin lowers plasma calcium concentrations by inhibiting osteoclastic activity. But salmon calcitonin must be administered more frequently than bisphosphonates, and some patients may become refractory to salmon calcitonin.[15]

Using bisphosphonates and salmon calcitonin in the same patient, either simultaneously or sequentially, is controversial. Experimental animals that received both did worse than animals receiving one or the other.[16] However, concurrent use of salmon calcitonin and bisphosphonates is the preferred treatment of emergency hypercalcemia of malignancy in people.[3]

Prognosis

The prognosis is good for animals that are decontaminated promptly or that receive treatment to decrease their serum calcium concentrations before soft tissue mineralization occurs. The prognosis is more variable if soft tissue mineralization has occurred. Soft tissue mineralization is minimally reversible and can lead to structural damage and decreased function of the renal, cardiovascular, gastrointestinal, and musculoskeletal systems. The amount of function loss and, thus, the prognosis depend on the duration and severity of the elevated plasma calcium X phosphorus product.[12] When animals present with signs of cholecalciferol toxicosis, inform clients of the seriousness of the situation and the cost and commitment required for treatment.

Table 1   Products Containing Cholecalciferol

Product Name	Concentration	Formulations
Quintox – Bell Laboratories	0.075% cholecalciferol	Pellets, seed mixtures, place packs
Rampage Motomco Ltd.	0.075% cholecalciferol	Pellets, place packs, bait chunks
Viactiv – Mead Johnson	100 IU (2.5 μg) vitamin D_3; 500 mg calcium; 40 μg vitamin K (per chew)	Chews flavored as milk chocolate, caramel, orange cream, or mochaccino
Multivitamins	Most products contain 400 IU (10 μg) of vitamin D_2 or D_3 (per tablet)	Tablets

Table 2   Expected Results of Parathyroid Hormone/Parathyroid Hormone-Related Peptide/Calcifediol Assay for Various Causes of Hypercalcemia

Disease	Parathyroid Hormone (serum)	Hormone/Parathyroid Hormone-Related Peptide (plasma)	Calcifediol (serum)
Cholecalciferol toxicosis*	Decreased	Absent	Increased
Hypercalcemia of malignancy*	Decreased	Present	Normal
Chronic renal failure*	Increased	Absent	Unknown (normal)
Primary hyperparathyroidism*	Increased	Absent	Unknown (normal)
Feline idiopathic hypercalcemia**	Normal	Absent	Unknown (normal)

*Source: Kruger, J.M. *et al.*: Hypernatremia and renal failure: Etiology, pathophysiology, diagnosis and treatment. *Vet. Clin. North Am. (Small Anim. Pract.) 26 (6):*1417-1445; 1996.
**Source: Midkiff, A.M. *et al*.: Idiopathic hypercalcemia in cats, *J. Vet. Intern. Med. 14 (6):*619-626; 2000.

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