Topical Review

Cholecalciferol

Michael E. Peterson, DVM, MS*, Kerstin Fluegeman, CVT

Reid Veterinary Hospital, Albany, OR, USA

*Address reprint requests to: Michael E. Peterson DVM, MS, Reid Veterinary Hospital, 933 SW Queen Avenue, Albany, OR, USA.

E-mail: petersonkate@netscape.net.

ABSTRACT

The primary source of exposure to cholecalciferol in dogs and cats is ingestion of rodenticide baits with vitamin D_3 as the active ingredient. Other sources of this toxin are human medications and rarely, contaminated pet food. Although the reported lethal dose 50% for cholecalciferol is 88 mg/kg, deaths have been seen with an individual exposure of 2 mcg/kg in dogs. Clinical signs are induced by profound hypercalcemia affecting multiple body systems. Clinical presentations may include anorexia, depression, muscle weakness, vomiting, polyuria, polydipsia, dehydration, abdominal pain, hematemesis, melena, and bradycardia. Tissue mineralization may develop if calcium $\times$ phosphorous product is greater than 60. Serum testing for hypercalcemia, hyperphosphatemia, and decreased serum parathyroid hormone are confirmatory. Initial treatment relies upon decontamination with emesis induction followed by administration of pulse-dose activated charcoal designed to interfere with the extensive enterohepatic recirculation of toxin. Medical management is designed to decrease serum calcium levels by use of intravenous fluid diuresis with administration of furosemide and prednisolone. Biphosphate pamidronate is used to inhibit calcium release from the bone. Phosphate binders aid in decreasing phosphate availability to interact with calcium. The prognosis is better if treatment is instituted early before development of hypercalcemia and hyperphosphatemia enables tissue mineralization to progress.

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Introduction

The 2 primary sources of dog and cat exposures to cholecalciferol are rodenticides or dietary supplements (either over the counter or prescription).[1,2] Changes in the Environmental Protection Agency regulations removed most second-generation anticoagulant rodenticides from the over-the-counter market in the United States. The effects of these regulations have been to encourage the marketing and over-the-counter purchase of other rodenticides such as cholecalciferol, bromethalin, and zinc phosphide for residential use and thereby increasing the probability of pet exposures to these toxins.

Dietary supplements are labeled in International units (IU) and 1 IU is equivalent to 0.025 µg of cholecalciferol (Vitamin D_3). Cholecalciferol rodenticides contain 0.075% or 0.75-mg cholecalciferol per kg of bait.

There have been clinical reports in the literature of over-fortified diets fed to both dogs and cats producing cholecalciferol toxicosis.[3]

Toxic Dose

There is a wide variation in individual susceptibility to cholecalciferol which is not necessarily dose dependent. The cause of this variation in susceptibility has not been clearly elucidated. Initial claims for rodenticide baits containing cholecalciferol promoted the wide safety margin for most mammals; however this has not been reflected clinically. Clinical signs have been seen in dogs with oral doses as low as 0.5 mg/kg. The oral lethal dose 50% has been reported to be 88 mg/kg in dogs, however lethal outcomes have occurred at exposures as low as 2 mg/kg.[1,4,5] Cholecalciferol (Vitamin D_3) is 10 times more toxic that vitamin D_2. Puppies are more sensitive than adult dogs; this situation is exacerbated as cholecalciferol and its metabolites are very lipophilic and therefore concentrate in the mother's milk.[1,4,6] Cats are more resistant than dogs.

The specific chronic oral cholecalciferol dose necessary to induce toxicosis in dogs and cats is unknown. However, dogs that are fed diets containing 50-100 µg/kg manifest clinical toxicosis within 2-3 weeks.[7] Several cats fed diets with elevated cholecalciferol levels developed toxicity.[3]

Toxicokinetics

Cholecalciferol is rapidly absorbed from the gastrointestinal tract and is carried from the blood to the liver by vitamin D–binding protein.[8,9] Hepatic cytochrome P-450 mixed function oxidase enzyme 25-hydroxylase rapidly metabolizes the parent compound to the principle circulating metabolite 25-hydrocholecalciferol (calcifediol).[10,11] After a single exposure, levels of calcifediol reach concentrations up to 20 times normal within 24 hours. This metabolic step is not regulated and is dependent upon the concentration of the substrate.

Calcifediol is then converted in the proximal convoluted tubule of the kidney by a mixed function oxidase enzyme 1-α-hydroxylase to 1,25-dihydroxycholeciferol (calcitriol).[10,11] This step is closely regulated. Calcitriol is the primary active metabolite. Peak concentration of calcitriol is achieved approximately 48-96 hours post–oral exposure. Primarily due to its tight regulation, calcitriol levels return to normal within one week of a single exposure.

Cholecalciferol and its metabolites are highly lipid soluble and therefore are slowly released from the body. The unregulated metabolic activity of the hepatic enzyme, 25-hydroxylase, converting these slowly released substrates makes the functional half-life of cholecalciferol extremely long, measured in months.[4,12]

The actual half-life of calcifediol is 15 days, however, owing to ongoing metabolism the functional half-life is 29 days.[10-12] The actual half-life of calcitriol is 4-8 hours but the functional half-life is 3 days.

Mechanism of Toxicity

Calcitriol (1,25-dihydroxyvitamin D) increases renal tubular reabsorption of calcium, increases calcium resorption from the bone, increases intestinal absorption of calcium (by increasing calcium-binding protein in enterocytes), and decreases parathyroid hormone synthesis. This results in an unregulated increase in plasma calcium and phosphorus. Once hypercalcemia and hyperphosphatemia reach levels where the calcium $\times$ phosphate product exceeds 60 (units must be in mg/dL) then metastatic mineralization of soft tissues will occur, particularly in the kidneys, intima of the large vessels, myocardium, and the gastrointestinal tract. Hypercalcemia directly affects cells by changing membrane permeability, decreasing cellular energy production, altering the calcium pumps, and inducing cellular necrosis. Hypercalcemia depresses vasopressin's influence upon renal tubules.

Clinical Signs

Clinical signs are induced by the 2 primary biochemical abnormalities of severe hypercalcemia and hyperphosphatemia. Clinical manifestations may be delayed 8-12 hours postingestion as the production of active metabolites progresses. The severity of the presenting clinical signs is a function of the rate of increase and the degree of hypercalcemia. These alterations cause acute renal tubular necrosis, gastrointestinal stasis, increased gastric acid secretion, decreased skeletal muscle responses, and decreased neural tissue responses.[1,8,9,12,13] Hypercalcemia induces some diuresis and loss of urine-concentrating ability of the kidney.[10,12] Afflicted dogs are often polyuric, polydipsic, and dehydrated. Elevations of gastric acid secretion and smooth muscle intestinal atony predispose to gastrointestinal hemorrhage. Intoxicated patients present with several of the following clinical manifestations including anorexia, lethargy, abdominal pain, hematemesis (gastric ulceration), melena, vomiting, and diarrhea. Cardiac arrhythmias may be exhibited as a bradycardia. Neurologic dysfunction leading to seizures may occur. Large exposures may present with clinical signs consistent with acute renal failure as early as 12-72 hours postingestion.

Minimum Database

Initial baseline laboratory values should include a complete blood count and serum chemistry. It is recommended that these tests be repeated daily at a minimum for the first 4 days in suspected cholecalciferol toxicosis. It is important that the sample not be lipemic or hemolytic as calcium levels will be incorrectly elevated. The ionized calcium is the biologically active component of total calcium. Calcium, phosphorous, blood urea nitrogen, and creatinine values are of particular interest. Hyperphosphatemia, sometimes as high as 20 mg/dL may occur 12-72 hours post–oral exposure. Hyperphosphatemia usually precedes hypercalcemia by up to 12 hours. Calcium $\times$ phosphorus product (mg/dL) may exceed 130 (values over 60 are at high risk of soft tissue mineralization). Urine specific gravity may become isosthenuric as the syndrome progresses.

It is recommended that serum calcium and phosphorus levels should be monitored for 5-7 days after they are normalized, then 3 times a week for 2 weeks.[13]

Young puppies and kittens will have elevated calcium $\times$ phosphorus products which may normally be higher than 60.

Confirmatory Test

Serum 25-hydroxycholecalciferol levels are elevated. Serum 1,25-dihydroxycholecalciferol levels are elevated. Postmortem histopathologic examination can be performed to search for evidence of mineralized soft tissues. Serum parathyroid levels are suppressed.[14,15] Serum testing for hypercalcemia, hyperphosphatemia, and decreased serum parathyroid hormone are confirmatory. Radiographic evidence of mineralization of soft tissues is indicative of elevated calcium levels and a calcium $\times$ phosphorus product (in mg/dL) greater than 60.

Treatment

A successful treatment strategy is based upon initial decontamination, controlling serum calcium levels, and decreasing serum phosphorus levels.

Decontamination

Recently exposed patients receiving a dose of 0.1 mg/kg or higher should be decontaminated.[13,16] Emesis induction should be performed if time from ingestion of toxin to presentation is less than 2 hours and the patient is not vomiting. Attempts at emesis induction should occur expeditiously owing to the toxins rapid uptake. Patients exposed greater than 2 hours before presentation should not have emesis induced as the effectiveness is poor after this period of time and onset of other therapies will be delayed. After 1.5 hours of ingestion, unless the block of rodenticide is still intact, the probability of removing significant quantities of toxin is poor. Even in the best of circumstances with early (within 10 minutes) emesis induction the maximum return is 75% of toxin. Emetics routinely administered in dogs include intramuscular administration of apomorphine at 0.04 mg/kg or peroral administration of 3% hydrogen peroxide at 1 mL/kg. In exposed cats, peroral administration of 3% hydrogen peroxide at 1 mL/kg or intramuscular or subcutaneous administration of xylazine at 0.4-1.1 mg/kg has been used successfully.[16]

Gastric lavage is no longer recommended in human medicine for decontamination as evidence for its efficacy is weak.[17]

Cholecalciferol has extensive enterohepatic recirculation and is therefore a prime candidate for pulse-dose activated charcoal therapy. The usual dose of activated charcoal is 1-4 g/kg, there is no evidence that added cathartics improve clinical outcomes in treating toxicities. Owing to the slow elimination of cholecalciferol subsequent lower doses of activated charcoal should be administered every 4-6 hours at 1 g/kg for a minimum of 24 hours.[5,13,16] The peroral administration of cholestyramine resin at 0.3-1 g/kg every 8 hours has been used successfully in human intoxications with cholecalciferol. This resin can be administered between activated charcoal doses, with charcoal followed 4 hours later with cholestyramine resin, followed 8 hours later with activated charcoal. The cholestyramine resin is administered for 4 days.[18]

There is some risk of hypernatremia after activated-charcoal administration, usually in smaller patients ingesting a toxin that causes high sodium levels or those patients with underlying renal dysfunction. In an attempt to mitigate this risk, many animals on a pulse-dose activated charcoal regime are placed on intravenous (IV) fluid therapy.

If the suspected intoxicated dog or cat has normal calcium, phosphorus, blood urea nitrogen, and creatinine on entry they should be decontaminated and these laboratory values should be

Table 1
Serum Markers in Differential Diagnosis of Vitamin D Toxicosis and Other Hypercalcemic Disorders in Dogs and Cats[4]

Disease	Ionized Ca	Total P	Intact PTH	25(OH)D$_3$	1,25(OH)$_2$D$_{33}$	Na/K Ratio
Cholecalciferol, vitamin D$_2$, or 25(OH)D$_3$ toxicosis	↑	↑	↓	↑	N	N
1,25(OH)$_2$D$_3$ or 1α(OH)D$_3$	↑	↑	↓	N	↑	N
Dihydrotachysterol, calcipotriene and analogues	↑	↑	↓	N	N	N
Malignancy	↑	N	↓	N	↓	N
Primary hyperparathyroidism	↑	N	↑	N	N	N
Granulomatous diseases (e.g., blastomycosis)	↑	↑	↓	N	↑	N
Hypoadrenocorticism	N*	N	†	N	N	↓
Primary renal failure	N*	↑	↑	N	N	N

Abbreviations: N, Normal; ↑, increased; ↓, decreased.

* Total serum calcium is increased.

† Not known.

reevaluated every 12 hours for a minimum of 4 days.[18] Elevations in phosphorus are usually the first indicator of toxicity. If no alterations from normal occur during the first 4 days, the patient may be released.[16]

Control Calcium Levels

The goal of medical therapy is to keep the plasma calcium × phosphate product less than 60 until the toxin is cleared. Techniques to lower calcium levels rely upon 2 strategies; first is to enhance the removal of excess calcium and second is to decrease calcium uptake from bone.

Administration of IV saline (0.9%) is preferred to correct any dehydration within the first 4 hours. Other fluids can be used but they do contain additional calcium. The hypercalcemia induces an osmotic diuresis that leads to dehydration and increases calcium reabsorption by the renal tubules. Maintaining fluid diuresis at 4-6 mL/kg/h (twice maintenance) prevents volume depletion and limits renal calcium reuptake. This fluid administration rate should be continued until serum calcium levels return to normal. Long-term fluid administration is not without risk and the patient should be monitored closely for evidence of hypokalemia and hypomagnesemia. Monitoring urine output is necessary and the patient should be monitored closely to prevent overhydration (obtain body weight several times daily).

The diuretic furosemide inhibits calcium reuptake in the ascending loop of Henle.[18,19] Once the patient's hydration status is corrected, the administration of an initial loading dose of 0.66 mg/kg of furosemide followed by a continuous rate infusion of 0.66 mg/kg/h can be instituted. Higher doses have been advocated but present significant challenges in maintaining fluid balance in the long term. Thiazide diuretics should not be employed as they are calcium retaining.[18]

Peroral administration of prednisolone 1-3 mg/kg every 8-12 hours can be administered to decrease bone resorption, increase calcium excretion, and decrease intestinal calcium uptake. However, it takes approximately 7 days to obtain maximum effect. There is some question as to the effectiveness of corticosteroids in combating cholecalciferol-induced hypercalcemia.

Historically 4-6 IU of calcitonin has been administered subcutaneously every 8-12 hours. The effects seem to be transient and calcitonin is often only effective for a couple of days.[13]

The alternative to calcitonin and currently the mainstay of hypercalcemia treatment is biphosphate pamidronate disodium. This drug inhibits osteoclastic calcium release from bone.[13,19] Pamidronate is administered at a dose of 1.5-2.0 mg/kg IV infusion of 150-250 mL 0.9% saline over 2-4 hours.[20,21]

Decrease Phosphate Levels

Phosphate binders such as aluminum hydroxide given perorally at 10-30 mg/kg every 8 hours are recommended until calcium and phosphate levels stabilize.[13]

Once serum calcium levels are normalized (usually a minimum of 1 week), IV fluid administration rates are slowly decreased with close monitoring of calcium levels. Prednisolone, furosemide, and phosphate binder (eg aluminum hydroxide) can then be administered perorally. Continue monitoring serum phosphorus and calcium levels; anorexia is an early clinical sign of increasing serum calcium.[13]

Prognosis

Prognosis is fair for those patients receiving treatment before soft tissue calcification develops. Once mineralization begins to progress, an accurate prognosis becomes much more difficult to establish. The degree of mineralization and renal damage set the prognosis. Medical management may be prolonged and owners should be aware of both the emotional and financial commitment necessary to treat these patients.

Differential Diagnosis

Differential diagnosis includes ingestions of synthetic vitamin D$_3$ ointments used in human medicine for the treatment of psoriasis such as tacalcitol or calcipotriene (Table 1). Other conditions inducing hypercalcemia include malignancy (e.g., lymphoma, perianal adenocarcinoma, and myeloma.), primary hyperparathyroidism, primary renal failure, and hypoadrenocorticism among others.[10,16-18]

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