Rodenticides containing cholecalciferol (vitamin D₃) are emerging as a popular consumer choice for eliminating rats and mice resistant to anticoagulant rodenticides. Ingestion of cholecalciferol rodenticides by dogs and cats can result in death. Toxic ingestions of cholecalciferol result in hypercalcemia (calcium level >12.5 mg/dL) and hyperphosphatemia (phosphorus level >7 mg/dL), with serum calcium levels reaching 20 mg/dL in some cases.¹² Even when treated, hypercalcemia may cause soft tissue mineralization, particularly in the heart, the kidneys, the gastrointestinal (GI) tract, and skeletal muscle.³ Subsequent heart, kidney, and multiorgan failure can result in chronic disease or in death.

Environmental Protection Agency (EPA) regulations (effective June 2011) limiting the sale, use, and packaging of long-acting anticoagulant (LAAC) rodenticides are expected to increase the use of cholecalciferol rodenticides and other non-LAAC rodenticides. These restrictions will likely decrease the use of LAAC rodenticides, such as brodifacoum and bromadiolone. Therefore, accidental ingestions of cholecalciferol rodenticides by domesticated pets are likely to increase. (It is currently too soon to assess the effects of the regulations.)

Understanding the fundamentals of cholecalciferol toxicosis is important for treating and managing accidental ingestion by pets. Cholecalciferol is manufactured and marketed as a rodenticide under a variety of brand names, most often in a 0.075% concentration. These products have a very narrow margin of safety: it takes only a small amount to cause severe toxicosis in dogs and cats. For example, ~0.5 tbsp of a pelleted 0.075% cholecalciferol product causes hypercalcemia in a 20-lb (9.1-kg) dog.²⁴ Therefore, ~1.5 tbsp would cause hypercalcemia in a 65-lb (Labrador-size) dog. A specific toxic dose has not been well established in cats.³⁵

**Triage**

During triage of patients presenting with rodenticide exposure, identifying the toxin often requires patience. Clients are justifiably upset after a pet ingests a toxin, so they may need help determining the active ingredient in a product. Product color, consistency, shape (e.g., pellets, blocks), and packaging may provide clues but should not be used as the sole means of identification. If the package is chewed or the label illegible, calling the manufacturer may help to determine the active ingredient and its concentration in the product. Identification is especially important because mis-treated or mismanaged ingestions can result in dangerous hyperphosphatemia, hypercalcemia, or acute renal failure.

Because cholecalciferol is not an LAAC, administration of vitamin K₁ (phytonadione) after accidental ingestion of cholecalciferol rodenticides is of no use. In fact, the mistaken use of vitamin K₁ for treating cholecalciferol toxicosis may result in death of a pet, especially if the serum calcium level is not evaluated and treated appropriately. Pet owners may say that a rodenticide package has the word vitamin on it. This comment should not be mistaken to mean the product contains vitamin K₁, which is often identified as an antidote on LAAC packaging. The mechanism of action of vitamin D₃ (cholecalciferol) is very different from LAACs, and accurate product identification is essential for appropriate treatment.

**Mechanism of Action**

Potentially toxic ingestions of cholecalciferol rodenticides result in overproduction of 25-hydroxycholecalciferol (a metabolite with limited activity) in the liver and 1,25-dihydroxycholecalciferol (an active metabolite) in the kidneys.³ Normally, cholecalciferol is
rapidly absorbed and converted unchecked to 25-hydroxycholecalciferol in the liver. Enzymes in the kidneys further convert 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol until there is a sufficient amount in the plasma. Feedback mechanisms then halt production of 1,25-dihydroxycholecalciferol, and levels of 25-hydroxycholecalciferol and calcium remain within normal limits. In an overdose situation, not only does conversion to 1,25-dihydroxycholecalciferol occur, but the 25-hydroxycholecalciferol concentration continues to rise until the plasma level is high enough for 25-hydroxycholecalciferol to become metabolically active. Elevated levels of 1,25-dihydroxycholecalciferol and, to a lesser extent, 25-hydroxycholecalciferol increase calcium absorption from the GI tract, increase calcium resorption from bone, and decrease calcium excretion by the kidneys. This results in hypercalcemia and hyperphosphatemia, which, left untreated, tends to produce (1) severe soft tissue mineralization—particularly in the heart, kidneys, lungs, and GI tract—in dogs and (2) pulmonary and soft tissue mineralization in cats.

The Clinical Picture
Cholecalciferol toxicosis can develop within 12 to 36 hours after an acute toxic ingestion. The most common clinical signs in dogs include anorexia, weakness, depression, polyuria, polydipsia, lethargy, vomiting, and diarrhea. Signs reported in cats include anorexia, vomiting, weakness, hypersalivation, polydipsia, halitosis, and lethargy. In both species, shock and bradycardia (with arrhythmias) have been reported. Death can result from acute renal failure or chronic soft tissue mineralization in the kidneys, heart, and other organs.

Baseline blood work should include a complete blood count, chemistry panel (including electrolyte levels), urinalysis (including specific gravity), and ionized calcium level measurement (if possible). Particular focus should be on the serum calcium, ionized calcium, phosphorus, blood urea nitrogen (BUN), and creatinine levels. Within the first 24 hours of a toxic ingestion, calcium and phosphorus levels begin to rise as high as 20 mg/dL and 11 mg/dL, respectively. These levels may increase simultaneously, or the phosphorus level may increase before the calcium level. The creatinine and BUN levels begin to rise within 48 to 72 hours in untreated animals. Urine should be examined for specific gravity, as it eventually becomes isosthenuric (specific gravity: 1.008 to 1.015) if the affected animal is not adequately treated. Blood work and urinalysis should be repeated every 12 to 24 hours for 72 hours in asymptomatic patients to assess for hypercalcemia, hyperphosphatemia, and azotemia. Symptomatic patients need to be monitored until all parameters are within normal limits.

Treatment
The goals of treating recent cholecalciferol rodenticide ingestion are to limit absorption and prevent hypercalcemia. After clinical signs have developed, the goals are to treat hypercalcemia and prevent or treat acute renal failure.

The mainstay therapy for rodenticide toxicosis is early and thorough decontamination. Emesis should be induced if exposure was recent and the patient is asymptomatic at presentation. If a large amount of rodenticide was ingested, gastric lavage may be necessary to fully evacuate the gastric contents. Once emesis has been induced or gastric lavage performed, activated charcoal with a cathartic (e.g., sorbitol) should be administered. Cholecalciferol recirculates through the liver and small intestine, so activated charcoal should be administered every 4 to 8 hours for 24 to 48 hours. When multiple doses of activated charcoal are given, only the first dose should contain a cathartic; otherwise, hypernatremia, severe free water loss, and diarrhea may develop.

The serum total calcium level should be kept at <12.5 mg/dL, the ionized calcium level at <5.4 mg/dL, and the phosphorus level at <7 mg/dL. If the total serum calcium level multiplied by the serum phosphorus level is >60 mg/dL, the risk is high for soft tissue mineralization, especially in the kidneys.

Intravenous 0.9% sodium chloride is used to promote diuresis and increase urinary excretion of calcium. Sodium chloride is preferred because it decreases the reabsorption of tubular calcium. If the patient does not have underlying cardiopulmonary disease, fluids should be administered at two to three times the maintenance rate. The use of calcium-containing, intravenous crystalloid fluids, such as lactated Ringer solution, should be avoided.

Calcium excretion by the kidneys can be enhanced by administration of furosemide and prednisone. Once the patient is well hydrated, furosemide should be administered as a 2- to 5-mg/kg IV bolus, followed by either intermittent boluses (2 mg/kg IV q4–6h) or a constant-rate infusion (0.5 mg/kg/h). Furosemide must be used carefully because, without appropriate fluid therapy, it can cause severe electrolyte changes and worsen azotemia. If injectable furosemide is not available, oral furosemide can be used if the patient is not vomiting. After stabilization, the patient should be sent home with 2 to 3 weeks of weaning doses of furosemide. Prednisone should be administered at 2 to 3 mg/kg q12h to aid calcium excretion. As with furosemide administration, the dose of prednisone should be slowly decreased within 2 to 3 weeks. GI protectants should be used if the dose of prednisone is high or the duration of treatment is long. Calcium-sparing diuretics, such as thiazides, should be avoided.

If hyperphosphatemia and hypercalcemia are present despite aggressive intravenous fluid therapy and administration of diuretics and corticosteroids, the use of a bisphosphonate, such as pamidronate disodium, should be considered. Bisphosphonates work by preventing normal and abnormal bone resorption. This medication is expensive but may be more economical than several weeks to months of conventional therapy. Pamidronate should be diluted in 0.9% sodium chloride and given at a rate of 1.3 to 2 mg/kg IV slowly for 2 hours. Typically, patients need only one dose of pamidronate; however, in rare, severe cases, a second dose can be given in 4 to 7 days. After administration of pamidronate, serum calcium and phosphorus levels should improve within 24 to 48 hours. Pamidronate has few reported adverse effects in animals: hypomagnesemia and arrhythmias occurred in one dog. Infusing pamidronate slowly over 2 hours decreases the possibility of renal toxicity.
Alternatively, salmon calcitonin can be given at a rate of 4 to 6 IU/kg SC q8–12h until the serum calcium level is <12.5 mg/dL. However, calcitonin is used less frequently than pamidronate because the former requires frequent dosing and may lead to the development of resistance. Typically, pamidronate and calcitonin are not used together; however, in rare circumstances in which response to one therapy is poor, using the other drug in combination can be considered. Both dosages are the same when the drugs are used together. It should be remembered that simultaneous administration of both medications may increase the risk of soft tissue mineralization.

Whether the patient is hospitalized or is treated on an outpatient basis, frequent monitoring of renal function and electrolyte levels is imperative. Calcium, phosphorus, BUN, creatinine, and ionized calcium levels should be evaluated every 12 to 24 hours during hospitalization and then every 2 to 3 days for the next 2 to 3 weeks. This can facilitate effective weaning of furosemide and prednisone therapy and detect secondary renal failure. If the patient remains asymptomatic after discharge, laboratory values should be checked one more time 1 month after the initial exposure; these values should be checked immediately if the patient deteriorates at any time after discharge.

Conclusion

As cholecalciferol rodenticides become more prevalent in the marketplace, education of veterinary professionals and pet owners regarding the associated risks and treatment options becomes more important. Ingestion of cholecalciferol rodenticides should be promptly recognized and treated. The prognosis is good if adequate treatment is initiated before hypercalcemia develops. Once an animal is hypercalcemic (calcium level: >12.5 mg/dL), the prognosis for full recovery is much worse. Soft tissue mineralization and chronic renal failure are known sequelae and may result in chronic illness or death, even after the serum calcium level returns to normal.

References

1. Clinical signs associated with cholecalciferol (vitamin D₃) toxicosis in dogs include
   a. vomiting and diarrhea.
   b. polydipsia.
   c. anorexia.
   d. all of the above

2. Which statement regarding cholecalciferol toxicosis is true?
   a. Clinical signs develop 12 to 36 hours after acute ingestion.
   b. Affected patients have a prolonged prothrombin time.
   c. The serum calcium level typically rises before the serum phosphorus level.
   d. The goal of treatment is to control bleeding.

3. For treating cholecalciferol toxicosis, administration of _______ can be considered.
   a. N-acetylcysteine
   b. pamidronate disodium
   c. phytonadione (vitamin K₁)
   d. fomepizole

4. If the patient remains asymptomatic after discharge, final laboratory values should be acquired _______ after the initial exposure.
   a. 48 hours
   b. 72 hours
   c. 1 week
   d. 1 month

5. In a 20-lb (9.1-kg) dog, ingestion of approximately _______ tbsp of a pelleted, 0.075% cholecalciferol rodenticide could result in hypercalcemia.
   a. 0.25
   b. 0.5
   c. 1
   d. 1.5

6. After correction of fluid losses, calcium excretion can be supported by administration of
   a. famotidine.
   b. furosemide and prednisone.
   c. ampicillin.
   d. metoclopramide.

7. Frequent monitoring of ____________ is important when treating exposure to cholecalciferol.
   a. prothrombin time
   b. ALT, AST, and ALP levels
   c. calcium, phosphorus, BUN, and creatinine levels
   d. venous blood gases

8. Which drugs should be avoided when treating cholecalciferol toxicosis?
   a. all antiemetics
   b. prednisone and furosemide
   c. all GI protectants
   d. calcium-sparing diuretics such as thiazides

9. The prognosis for cholecalciferol toxicosis is good if treatment is initiated
   a. within an hour of ingestion.
   b. before hypercalcemia develops.
   c. before the BUN level rises.
   d. at any time and is aggressive.

10. Because of recent EPA regulation changes, the use of LAAC rodenticides is likely to
    a. increase over time.
    b. decrease over time.
    c. remain the same.
    d. cease immediately.