Arlo's Odds ARe LOw

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Introduction

Cleaning supplies and chemicals in and around the house have caused a real problem for pet owners. Many of these products contain potent smells that attract household animals, dogs especially. One important toxin is rodenticide (rat bait). Over the years rodenticide toxicity has become a bigger problem for veterinarians, as companies have developed more toxic ingredients and multiple different types of rodenticides. Types include anticoagulant, neurotoxic, and cholecalciferol-based products. Cholecalciferol, also known as vitamin D3, is a component of the calcium regulatory system in the body. High levels of cholecalciferol can lead to problems associated with all organs, especially the kidneys, gastrointestinal tract, and bone. Early diagnosis and treatment of cholecalciferol rodenticide toxicity is important to optimize the long-term outcome for the animal.

History and Presentation

A known history of consumption of cholecalciferol containing items, specifically rodenticide, is by far the easiest way to establish a diagnosis. However, if there is not a known consumption, dogs commonly present with gastrointestinal signs including vomiting and diarrhea (which may have blood or melena). If animals present later in the disease process, they may show signs of acute renal failure or multi-organ failure due to soft tissue mineralization throughout the body.

In this case, Arlo is a 6-month-old male intact Goldendoodle who presented to the Mississippi State University College of Veterinary Medicine (MSU CVM) on May 28, 2021, for known cholecalciferol toxicity. Arlo ingested D-CON rodenticide containing cholecalciferol on Tuesday, May 25. His owners noted that there were 18 containers of rodenticide in the house.

Arlo presented to his primary veterinarian on Wednesday, May 26, where emesis was induced, and bloodwork revealed a hypercalcemia and hyperphosphatemia. Arlo received activated charcoal with sorbitol, a 7.9 mg/kg prednisone equivalent of Dexamethasone SP, and he was started on 0.9% NaCl at a 3x maintenance rate. Arlo began urinating blood and was referred to MSU CVM.

On presentation Arlo was quiet, alert, and responsive. He weighed 5.7 kgs and had a body condition score of 4/9 (with 4-5/9 being ideal). Arlo's vital signs were: heart rate of 92 bpm, a rectal temperature of 102.6 º F and a respiratory rate of 60 breaths per minute. His mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. There were ulcers along the majority of his upper gum surfaces of his mouth that were pale pink to tan in color and raised, varying in size with the largest being approximately 1.5 cm X 1.5 cm. Arlo's eyes, nose, and ears were clear with no ocular or nasal discharge noted and minimal waxy debris in his ears. No crackles, wheezes or murmurs were heard upon cardiothoracic auscultation; however, his cardiac sounds were muffled and difficult to auscultate. His femoral pulses were strong, and his peripheral lymph nodes were soft, small, and symmetrical. Mild pericardial effusion was present surrounding the heart and AFAST revealed free fluid surrounding the right kidney in the hepatic renal quadrant and in the cecal-colic quadrant. A series of blood pressure readings were as follows: 115/65 (84), 121/73 (86), and 122/77 (89). The remainder of Arlo's physical exam was unremarkable. Shortly after Arlo's triage exam, he urinated, and the urine appeared to be normal in color. He vomited a dark red blood-tinged mucous.

Diagnostic Approach

Initial diagnostics for cholecalciferol toxicity should focus on evaluating calcium and phosphorus levels. A complete blood count (CBC), serum chemistry including electrolytes, and an ionized calcium can determine the severity of hypercalcemia and azotemia. Abdominal radiographs and ultrasonography are helpful to evaluate for free abdominal fluid and determine the amount of damage related to the gastrointestinal tract. If indicated, further diagnostics including CT can be used to determine if mineralization of any organs has occurred.

Initial diagnostics for Arlo revealed a hypercalcemia (with his total calcium at 12.2 mg/dl and ionized calcium level at 1.77 mmol/L), hypokalemia (3.4 mmol/L), hyperphosphatemia (8.6 mg/dl) and an increased blood urea nitrogen (BUN) at 74 mg/dl. Abdominal radiographs revealed moderate gastrointestinal mineralization.

Pathophysiology

The pathophysiology of calcium regulation in the body is incredibly complex. Levels are very closely maintained by mainly the "intestine, kidney, and bone"[4] and any slight change out of the normal range can be concerning.[4] Normal ionized calcium ranges from 1.2-1.5 mmol/L in dogs.[4] Parathyroid hormone (PTH) and vitamin D metabolites deal with increasing plasma calcium levels mainly by pulling calcium from bone and increasing calcium reabsorption from the kidneys and intestine using multiple different pathways. Calcitonin is another important regulator that decreases plasma calcium levels in response to hypercalcemia. It does this by preventing calcium from being broken down in the bone.[4]

In the case of cholecalciferol containing rodenticide toxicity, vitamin D3 (cholecalciferol) is ingested. It is then converted into 25-hydroxycholecalciferol (calcifediol) in the liver by 25-hydroxylase. Next, the kidneys convert calcifediol into 1,25-hydroxycholecalciferol (calcitriol)

using 1-alpha-hydroxylase.[2,3,4] It is important to note that calcitriol has a strong negative feedback loop, meaning that once certain levels of calcitriol are produced 1-alpha-hydroxylase stops creating more calcitriol. Calcifediol does not have a strong negative feedback loop, so levels of it will continue to rise and in turn raise the plasma calcium levels even further.[3] This occurs because calcifediol and calcitriol cause more calcium absorption from the intestines and promote phosphorus and calcium breakdown in the bones.[3,4] High levels of plasma calcium can lead to cell death by damaging the membrane permeability and decreased energy production. Damage most commonly occurs in the kidneys, intestinal tract, and bone, however high calcium X phosphorus levels "greater than 60 mg/dl" can lead to soft tissue mineralization.[2,4]

Differential Diagnoses

When there is not a known ingestion of rodenticide, other differentials for hypercalcemia should be ruled out. Hypercalcemia of malignancy, hyperparathyroidism, and chronic renal failure can be ruled out by send-out bloodwork to measure levels of cholecalciferol, calcifediol, PTH, and PTH-rp.[2,3] Cholecalciferol toxicity will show an elevated calcifediol with a decreased PTH and absent PTH-rp. Hypercalcemia of malignancy should have an elevated PTH-rp and chronic renal failure should have an increased PTH.[3]

Treatment and Management Options

Animals that present within hours of ingestion should be induced to vomit using apomorphine at 0.04 mg/kg IM.[2] In an animal that is alert and responsive, activated charcoal at "240 ml commercial slurry per 25- to 50-lb"[3] can also be given to bind to the toxin and decrease the amount of gastrointestinal absorption. Baseline BUN, creatinine, calcium, and phosphorus

levels should be measured and monitored for multiple days. If the patient presents past the point of decontamination, measures should be taken to decrease calcium levels and excrete calcium from the body. Fluid diuresis using 0.9% NaCl is suggested because it lacks calcium in the fluids.[2,3,4] Furosemide can be administered following re-hydration as it "inhibits calcium reuptake in the ascending loop of Henle"[2] leading to calcium excretion in the urine. Other drugs used to decrease plasma calcium levels include corticosteroids, calcitonin, and bisphosphonates, specifically pamidronate disodium. Pamidronate disodium prevents mobilization of calcium from the bone.[2,4,5] Phosphate binders can also be administered to decrease concurrent plasma phosphorus levels to lessen the chance of soft tissue mineralization.[2]

Arlo was treated supportively for several days using 0.9% NaCl and Plasmalyte fluid therapy, furosemide, gastroprotectants (including sucralfate, ondansetron, pantoprazole, and metoclopramide), Cerenia, methadone, N-acetylcysteine, Yunnon Baiyan, and the bisphosphonate Zoledronic acid. Arlo continued to vomit and regurgitate blood-tinged fluid for several days, and he was placed on a CRI of metoclopramide and famotidine, along with high dose antiemetics which eventually stopped his constant vomiting. An ultrasound and CT of his abdomen were performed, and Arlo had severe gastritis and considerable mineralization of his gastrointestinal tract, kidneys, and most other organs. A few days after being in hospital, Arlo developed aspiration pneumonia diagnosed via thoracic radiographs, and his oxygen saturation on room air decreased. Arlo was placed in the oxygen cage, started on unasyn, and nebulized multiple times per day. A nasogastric feeding tube was placed, and Arlo received a CRI of vivonex liquid nutrition along with water into his NG tube. A jugular catheter was also placed. Arlo had significant gastrointestinal bleeding and received a blood transfusion to treat his anemia. After about a week of supportive care Arlo was able to oxygenate normally on room air

and he stopped vomiting and regurgitating. He was removed from the oxygen cage, began eating normally, and his liver and kidney values normalized. His ionized calcium levels peaked (at 1.95 mmol/L) and began decreasing at this time. Over the next week Arlo's mentation brightened and he ate multiple times per day without vomiting. He was diagnosed with Stage 1 Kidney Disease, as his urine protein/creatinine ratio was markedly increased at 3.3 (normal range being < 0.5), but he was not azotemic off of fluid therapy. Arlo was sent home on oral metoclopramide, Clavamox, ondansetron, cisapride, sucralfate, and Cerenia, with instructions to also purchase esomeprazole over the counter. He was slowly weaned of his gastrointestinal medications, and we recommended regular recheck examinations with his referring veterinarian to evaluate his calcium and kidney levels.

Expected Outcome and Prognosis

Outcome and prognosis for cholecalciferol toxicity depends on the amount ingested and the time frame between ingestion and beginning treatment. According to a topic review, the “oral 50% lethal dose has been reported to be 88 mg/kg in dogs, however lethal outcomes have occurred at exposures as low as 2 mg/kg”.[2] The higher the calcium and phosphorus levels are able to rise in the body, the more tissue mineralization and damage is possible. If emesis and decontamination is achieved before the animal’s calcium levels rise, prognosis for a full recovery is better.[4] If plasma calcium levels rise and the animal presents already showing signs of acute renal failure including polyuria, polydipsia, isosthenuria, and azotemia, or the animal already has tissue mineralization, the prognosis to recover organ function is poor.

Conclusion

To summarize, early diagnosis and aggressive treatment of rodenticide containing cholecalciferol is crucial in aiding patient outcome. Calcium is a major electrolyte in the body responsible for many cellular functions and it is closely regulated by the intestines, kidneys, and parathyroid gland. Treatment of toxicity using decontamination immediately after ingestion is the best way to ensure that calcium does not rise to lethal levels, and aggressive treatment using fluids, gastroprotectants, furosemide, and bisphosphonates are important to quickly lower calcium levels. Arlo is an incredibly lucky dog to have considerable kidney and gastrointestinal mineralization on his CT and still have relatively normal bloodwork values. Arlo has returned to his normal life thanks to the swift and aggressive treatment performed by MSU CVM.

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