Bud Johnson

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INTRODUCTION:

As a species, dogs have an undeniable way of putting their nose, mouth, and inevitably, their stomach in places they shouldn't be. And humans, as a species, do not have a particularly high tolerance for rodents invading their living spaces. Because of these dilemma's, veterinarians commonly find themselves faced with treating an animal who has inadvertently ingested rodenticides.

Currently, on the market, there are three major ingredients comprising most rodenticides. There are those that work as anticoagulants (bromidalone, chlorophacinone, difethialone, diphacinone, brodifacoum, and warfarin), neurotoxins (bromethalin), and vitamin D analogues (cholecalciferol). All of these may be toxic to dogs at variable doses. In order to promote ingestion by rodents, these toxins are flavored, which also happens to attract dogs. Treatment of each rodenticide is vastly differently, making it imperative to differentiate the active ingredient when treating a dog with a known history of ingestion.

HISTORY AND PRESENTATION:

Bud Johnson is an approximately four-year-old neutered male chocolate Labrador retriever who presented to Mississippi State University College of Veterinary Medicine Internal Medicine Service after ingesting approximately 140 grams of a cholecalciferol-based rodenticide (d-Con). The ingestion occurred at approximately 5:30 AM on the morning of September 6, 2018. Two hours following ingestion, Bud's owner brought him to his primary veterinarian at Dilworth Small Animal Hospital. At Dilworth, vomiting was immediately induced using apomorphine. Bud vomited up his breakfast, a small amount of paper, and seven of the ten small bags of rodenticide reportedly ingested. The bags were chewed and did not appear to contain any

of the rodenticide. At this time, it was determined that the rodenticide ingested contained cholecalciferol, a vitamin D analogue.

Baseline blood work and a urinalysis were performed. All values were within normal limits, including his ionized calcium. An intravenous catheter was placed, and Bud was started on NaCl 0.9% at 330 ml/hr (3x maintenance). In an effort to begin decontaminating and combatting the side effects of the rodenticide, Bud received activated charcoal with sorbitol orally. In addition, dexamethasone SP and Cerenia were administered intravenously. Due to the large amount of rodenticide ingested and unproductive decontamination, it was recommended that Bud Johnson be referred to Mississippi State University College of Veterinary Medicine for further treatment and around-the-clock care.

Bud Johnson has a history of heartworm disease, pancreatitis, and raisin ingestion- all of which were treated successfully. He had a few seizures in the last 18 months, but treatment was not currently required. He has been diagnosed with hypothyroidism for which he takes levothyroxine twice daily. Due to his anxious nature, he also receives 40 mg of fluoxetine twice daily.

CASE SUMMARY:

On presentation, Bud Johnson was anxious, alert and responsive. He weighed 32.2 kg (64.4 lbs) with a body condition score of 4/9 (ideal). He was hyperthermic with a temperature of 104.9 °F, likely due to his anxious state. His tachycardic at 100 beats per minutes with a normal sinus rhythm. He was actively panting so a precise respiratory rate could not be collected. His mucous membranes were red and tacky, with a capillary refill time of 1 second. His heart auscultated normally; no murmurs were appreciated. His lungs auscultated normally in all four

quadrants. tFAST showed that his pleural space was free of fluid. He was mildly reactive during palpation of his abdomen; however, this seemed more likely due to anxiousness than pain. aFAST revealed no free fluid in his abdomen. Overall, Bud's mentation was very anxious, he appeared to be slightly trembling and was hyperreactive. At the time of his initial physical exam, his history of seizures was unknown, therefore, consideration of his hyperreactivity and trembling was given to a possible post-ictal episode or manifestation of cholecalciferol toxicity.

Initial bloodwork revealed a mild respiratory acidosis. His sodium was increased, likely due to the activated charcoal and 0.9% NaCl intravenous fluid administration. His ionized calcium levels were low normal. Bud was started on intravenous fluids and placed in ICU for around the clock monitoring. Bud Johnson was started on prednisone and furosemide to promote diuresis and calciuresis. His ionized calcium and renal values remained stable overnight.

On the morning of September 7, Bud Johnson's ionized calcium levels slightly increased, but remained within normal limits. His potassium levels had decreased due to the high rate of fluid administration, prompting supplementation of his intravenous fluids with potassium chloride. Throughout the day, Bud Johnson was extremely lethargic, anorexic, and depressed. A chemistry panel revealed a mildly elevated creatinine and slightly increased phosphorous. His potassium levels were slightly increased with the supplementation of his fluids, but were still below the reference range. Later that evening, NOVA results showed a normal calcium and creatinine. At this time, Bud Johnson was started on an appetite stimulant, since he had not seemed interested in food since admission.

Bud Johnson's calcium levels stayed within normal limits the remainder of his stay. His appetite continued to improve, and his creatinine levels never increased to a point where they

were out of the normal range. As he continued to improve clinically, his fluids were slowly weaned. His bloodwork remained stable throughout the tapering of his intravenous fluids.

At the time of discharge, Bud Johnson continued to appear bright and all NOVA and blood chemistry values were within normal limits. On the day of discharge, he received a dose of pamidronate over the course of 2 hours as an additional therapy for his cholecalciferol toxicosis.

Bud Johnson returned to Mississippi State University College of Veterinary Medicine two additional times since discharge. Four days following discharge his ionized calcium levels remained stable; however, his phosphorous levels were high normal. For this reason, Bud Johnson's owners were instructed to give aluminum hydroxide once daily until his next recheck. A week later, Bud Johnson returned. His serum chemistry was within normal limits, including his calcium, phosphorous, BUN, and creatinine levels. At this time, Bud Johnson was no longer required to recheck with the internal medicine department and went home to live a long happy life.

PATHOPHYSIOLOGY:

Cholecalciferol, also known as Vitamin D_3, has become an increasingly common ingredient found in commercial rodenticides, with popular brands such as D-con recently switching from anticoagulant based ingredients to cholecalciferol[1]. Other brand names to watch out for are Quintox, Rat-B-Gone, and Rampage[1]. These rodenticides were initially marketed in the 1980's claiming it was "safe for use around dogs". Initial laboratory studies revealed an LD50 of 88 mg/kg, however, once on the market, toxic doses were found to be much lower (0.5 mg/kg) [1]. Most formulations consist of 0.075% cholecalciferol, meaning a fifty-pound dog would only need to ingest half an ounce of the rodenticide for it to be deadly[1]. For this reason, it is

important to recommend treatment even when only a small amount of rodenticide has been ingested[1].

Once ingested, cholecalciferol is quickly absorbed and through enterohepatic recirculation is converted to calcifediol (25-hydrocholecalciferol) in the liver by 25-hydroxylase[1]. Calcifediol is then metabolized by the kidney to calcitriol (1,25-hydroxycholecalciferol) by 1 – alpha - hydroxylase[1]. Of cholecalciferol and it's two metabolites, calcitriol is the most metabolically active due to its increased affinity to vitamin D receptors on target organs (bone, gastrointestinal tract, and kidneys), leading to increased calcium and phosphorous absorption[1]. All metabolites are lipid soluble and stored in fat tissue, increasing its length of bioavailability and effects on the body[1].

In toxic situations, calcifediol (the first metabolite produced by the liver) levels remain increased for a prolonged period of time despite normal calcium levels[1]. Since calcium levels are initially normal, 1-alpha-hydroxylase is down regulated in the kidney, decreasing the conversion of calcifediol to calcitriol[1]. Unfortunately, 2-5-hydoxylase's negative feedback system is less sensitive, and cholecalciferol continues to be converted to calcifediol in the face of normocalcemia[1]. While calcitriol levels are decreasing, calcifediol continues to increase. Although calcifediol is known to have less affinity for vitamin D receptors, it becomes increasingly active in the absence of calcitriol[1]. This situation leads to a hypercalcemic and hyperphosphatemic state, and when not promptly corrected, can be lethal[1].

Clinical manifestations in patients with unknown history or delayed knowledge of the toxicosis become apparent 24-72 hours after ingestion. These clinical signs typically include anorexia, depression, vomiting, and diarrhea[1]. If enough cholecalciferol has been ingested, patients may present in acute renal failure. This is initially due to dystrophic calcification,

occurring secondary to necrosis, of the renal tubules. At this advanced stage patients may be bradycardic[3], sensitive during abdominal palpation, polyuric and polydipsic[1]. Serum chemistry may reveal a severely increased serum calcium accompanied by a moderately increased phosphorous, with a Ca X P product exceeding 100 mg/dl. In cases where Ca x P product exceeds 60-70 mg/dl, mineralization of major organ systems including the kidneys, gastrointestinal tract, liver, myocardium, blood vessels, and other soft tissues will occur[3]. Mineralization of these organs results in a disruption in function, leading to a physiologic state that is not conclusive with life[3]

DIAGNOSIS:

In an attempt to confirm toxicosis, it is important to rule out other causes of hypercalcemia. Alternative diagnoses to consider in hypercalcemic patients are hypercalcemia of malignancy, Addison's, primary hyperparathyroidism, chronic renal failure, and ingestion of human prescription products[3]. A thorough history should be acquired with specific questions regarding any supplements, prescriptions, topical vitamin D products containing talcalcitol and/or calcipotriol[5]. Additionally, vitamin D toxicity has been associated with misformulations of dog foods. A parathyroid hormone/parathyroid hormone related peptide/calcifediol assay can be utilized to help with confirmation. This test would reveal increased serum calcifediol with decreased PTH levels and absent parathyroid related hormone when dealing with cholecalciferol toxicity[3].

TREATMENT:

When faced with a patient with a known or suspected history of cholecalciferol rodenticide ingestion, induction of emesis using apomorphine should be performed within the first 4-6 hours post-ingestion[4]. In canine patients, this can readily be achieved using apomorphine. Identification of the toxin should be attempted, however, despite decontamination of the stomach contents, further treatment should be pursued due to the low toxic dose. Gastric lavage may be attempted in an effort to fully evacuate stomach contents if emesis is not successful[4].

Following emesis and/or gastric lavage, activated charcoal with sorbitol should be administered orally in an effort to bind the remaining toxin and reduce absorption within the gastrointestinal tract. Initial dosing should be between 1-4 mg/kg[4]. Additional doses of 0.5-2 kg mg/kg, without sorbitol, should be administered every 8 hours for 48 hours[5].

The patient should be started on intravenous fluid therapy. NaCL 0.9% is recommended at two to three times maintenance in an effort to promote diuresis and calciuresis. To further promote calciuresis, furosemide should be administered at 5 mg/kg IV and continued at 1-5 mg/kg orally every 12 hours thereafter[4]. If dehydrated, furosemide should not be administered until their hydration status is corrected. Prednisone is an additional adjunctive treatment used for its ability to decrease calcium absorption in the gastrointestinal tract and increase secretion of calcium at the kidney[4]. If phosphorous levels are increased at this time, phosphate binders should be utilized to reduce absorption from the gastrointestinal tract[4].

Patients should remain in hospital on fluids and above stated treatments for a minimum of 4 days. At this point, clinical signs would have become apparent[3]. While in hospital chemistry panels should be run at least every twenty-four hours to monitor ionized calcium, phosphorous

levels, blood urea nitrogen, creatinine[3]. As fluid therapy is decreased, calcium levels should be closely monitored[3].

If patients remained normocalcemic throughout the entirety of treatment, no further treatment is required, they may be discharged. However if patients remain hypercalcemic despite decontamination and initial treatment, therapy may need to be continued for up to a month[6]. At this point, two additional medications should be considered. The first of which is pamidronate disodium. Pamidronate disodium works as a bisphosphonate which lowers serum calcium levels by inhibiting bone resorption of osteoclasts[6]. Bisphosphonates reduce calcium 24-48 hours after administration, allowing for outpatient treatment of stable patients[6]. Following initial administration, serum calcium levels should be rechecked. If needed, and additional dose of pamidronate can be administered 5-7 days after.

If pamidronate is not available, a second option is salmon calcitonin. This drug is a synthetic polypeptide, similar to autogenous calcitonin, that works similarly to pamidronate by reducing the resorptive capacity of osteoclasts[2]. This drug requires dosing every 2-3 hours until the patient becomes normocalcemic[2]. Because patients have become refractory to treatment and its efficacy has been unreliable, this drug is preferred second to pamidronate[6].

Post-mortem diagnosis gross necropsy finding include mineralization of major organs including the kidneys, gastrointestinal tract, liver, myocardium, blood vessels, and other soft tissues. These deposits appear chalky and white. Overall, prognosis is good for animals with known exposure and prompt treatment. However, once animals develop clinical signs, their prognosis worsens[5].

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