Dukes of “Hazard”

Katie Y. Sanford

Mississippi State University

College of Veterinary Medicine

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Advisor:

Rebecca Watkins, DVM

Assistant Clinical Professor

Introduction:

Rodenticide toxicity is an unfortunately common small animal toxicity that is seen primarily in private practice. In severe cases, these patients can be referred to hospitals for advanced treatment. There are two major categories of rat bait: anti-coagulant and non-anti-coagulant. Anti-coagulant rat bait sources are more frequently seen; however, they have been taken off the market for commercial use due to development of rodent resistance leading to development of non-anti-coagulant rat bait sources. The mainstay of treatment for anti-coagulant rodenticide toxicity is vitamin K supplementation, but can progress to plasma transfusions and whole blood transfusions. The pathophysiology behind rodenticide toxicity, anti-coagulants in particular, are well understood and are divided into first and second generations with the second generation rodenticides being more devastating.

History and Presentation

Beau and Luc are 1.5 year old male neutered Great Pyrenees that presented to MSU Emergency Services on November 24, 2020 for consuming rat bait. They both presented to their primary care veterinarian on November 11, 2020 for abnormal clinical signs; however they had two different clinical presentations. Beau was wheezing and lethargic at home with labored breathing. There was dried blood crusted around his nares on the right side, but no petechiation or obvious hemorrhage. Luc had been coughing for two days and recently started coughing up blood. He had blood tinged saliva and mild hemorrhage from his oral mucosa upon presentation to the primary veterinarian. Luc also had petechiation in the right axillary region. After gathering further history, the owner mentioned she had set out “Just One Bite II Bars” one week prior to the development of the patients signs leading to the diagnosis of rodenticide toxicity.

The primary care veterinarian then performed bloodwork on both dogs. Beau's blood work revealed a severe normocytic hyperchromic regenerative anemia, moderate mature neutrophilia, mild lymphocytosis, and mild basophilia. He had a hematocrit of 17% and a clotting time of 40 minutes. It is important to note that the primary care veterinarian based both patient's clotting time on how long it took the blood to clot in a red top tube. No coagulation profile or buccal mucosal bleeding time (BMBT) was performed. On Luc's bloodwork, it revealed a mild thrombocytosis, mild mature neutrophilia, mild lymphocytosis, and mild basophilia. However, Luc had a hematocrit of 39% and a clotting time of 14 minutes. The primary care veterinarian had one bag of 240 mls fresh frozen plasma (FFP) in stock, which expired September 6, 2020. The owner was made aware that the clotting factors in the expired FFP may not be labile or active, but it was elected to not split up the bag and give the one bag all to Beau since his hematocrit was severely decreased and had a severely prolonged clotting time. Beau also received 20 mls (200 mg) of subcutaneous vitamin K supplementation. Luc's bloodwork was not as severe as Beau's so he did not receive the expired FFP, but he did receive 20 mls (200 mg) of subcutaneous vitamin K supplementation. Both Beau and Luc were then referred to MSU for further treatment due to unavailability of fresh frozen plasma.

Upon arrival to MSU Emergency Services, the sibling brothers had different presentations. Beau was quiet, alert, responsive. He had a heart rate of 140 bpm, respiratory rate was not obtained due to panting, temperature was 102.0 F, and weighed 39.3 kg. His mucous membranes were pale pink, moist and capillary refill time was less than two seconds. His heart and lungs auscultated normally with no wheezes, crackles, murmurs, or arrhythmias. His respiratory effort on expiration was slightly increased. His abdomen was tense on palpation, but no pain, masses, or organomegaly was noted. Eyes, ears and nose were normal in appearance and

had no discharge or blood. Femoral pulses were bilaterally strong and synchronous. No petechiation or evidence of hemorrhage were appreciated. All other physical exam parameters were within normal limits.

On Luc's presentation, he was bright, alert, responsive. His heart rate was 156 bpm, respiration was not obtained due to panting, temperature was 102.4 F, and weighed 39.7 kg. His mucous membranes were pale pink, moist and capillary refill time was less than two seconds. His heart and lungs auscultated normally with no wheezes, crackles, murmurs, or arrhythmias. His abdomen was tense on palpation, but no pain, masses, or organomegaly was noted. Eyes, ears and nose were normal in appearance and had no discharge or hemorrhage. However, Luc did have hemorrhage from his oral mucosa. He also had petechiation still evident in the area of his right axillary region. Femoral pulses were bilaterally strong and synchronous. All other physical exam parameters were within normal limits.

Diagnostic Approach:

Both patients had a triage exam, coagulation profile, and a complete blood count performed. Beau's triage exam revealed a few abnormalities. AFAST revealed a scant amount of fluid in the hepato-renal quadrant and, within the bladder, there was a mass effect. Differentials being hematoma, neoplasia, and bladder sludge. The TFAST revealed a scant amount of pleural effusion. Blood pressure readings were all moderately elevated; however, he was anxious during the exam. His SpO2 was normal at 98%. Beau had a normal coagulation profile with a Prothrombin Time (PT) of 9.6 (5.0-12.0) and Partial Thromboplastin Time (PTT) 15.1 (10.0-20.0). The improved values are thought to be the result of him receiving the expired FFP from the primary veterinarian. His complete blood count revealed a mild to moderate leukocytosis with a white blood cell count of 25.81 (5.00-14.20), mature neutrophilia of 22,712 (3,100-

11,800), severe thrombocytopenia of 67 (159-455), regenerative left shift of 774 (0-400) and lymphopenia normocytic normochromic anemia of 2.65 (5.60-7.90).

Luc's triage exam revealed no abnormalities. He was negative for any free fluid or abnormalities on AFAST and TFAST. Blood pressure readings were slightly elevated similar to his brother; however, he was also anxious during his exam. Luc had an abnormal coagulation profile. His PT was severely prolonged at 72.2 (5.0-12.0) and his PTT was mildly prolonged at 22.4 (10.0-20.0). Luc's complete blood count revealed a mild leukocytosis of 17.85 (5.0-14.20), severe lymphopenia of 178.5 (1,100-4,800), mild thrombocytopenia of 157 (159-455) and a moderate mature neutrophilia of 16,600 (3,100-11,800). The blood work obtained and interpreted at MSU confirmed that both patients were still affected; however, Luc was now at risk of becoming worse than Beau.

Pathophysiology:

Rodenticide toxicity is a common small animal toxicity seen more frequently in dogs; however, cats can also be affected. It is not species specific and animals of any age can be affected. It has been reported that the toxic dose of anticoagulants to mammals range from 0.02-0.5 mg/kg. This is why anti-coagulants have either single dose or multi-dose toxic feedings. There are two general categories of rodenticides: anticoagulant and non-anticoagulant. Anticoagulants are generally more commonly seen than non-anticoagulants; however, anticoagulants are being taken off the market and non-anticoagulant rodenticides are becoming more frequently seen. The first rodenticide created was Warfarin, a multi-dose first generation anticoagulant created from moldy sweet clover. Overtime, rodents have developed resistance, making warfarin a less effective rodenticide. Since then, other anticoagulant rodenticides have been developed along with non-anticoagulant rodenticides, which have a separate pathogenesis.

Anticoagulants are divided into two major classes: first generation and second generation. First generation anticoagulants include Warfarin, Diphacinone, and Chlorophacinone. They have a short half-life and have a short tissue persistency averaging about one week. Second generation anticoagulants include Difenacoum, Brodifacoum, and Bromadiolone. Beau and Luc consumed "Just One Bite II Bars" which contain the active ingredient, Bromadiolone, which is a single dose toxicosis. Second generation anticoagulants are considered "superwarfarins" because their half-life is significantly longer as well as their tissue persistency. The tissue half-life of second generation anticoagulants range from 16-220 days. This is crucial to remember when determining the treatment course, as the duration can last for several weeks. Owners must also be educated and understand the importance of having bloodwork re-evaluated and continuing treatment. Both generations of anticoagulants target vitamin K dependent clotting factors, which lead to severe and/or fatal complications.

Vitamin K dependent clotting factors include factors II, VII, IX, and X. Each of them are an integral component in the clotting cascade. Clotting factors are produced by the liver, which is targeted by anti-coagulants. Normally, vitamin K_1 is converted to vitamin K_1 epoxide, which is then converted by vitamin K_1 epoxide reductase back into the active form of vitamin K_1. This cycle is repeated to create active clotting factors that circulate in the bloodstream. Anticoagulants act on vitamin K_1 epoxide reductase to inhibit the conversion to the active form, which leads to depletion of clotting factors and cause a true deficiency in less than 24 hours post-consumption. Hemorrhage can occur as soon as any circulating clotting factors are consumed because there are no more clotting factors being made to be replaced in the blood stream.

The clotting cascade is divided into three pathways: intrinsic, extrinsic, and common pathways. Factor IX functions in the intrinsic pathway. Factor VII functions in the extrinsic

pathway. The last two factors II and X are apart of the common pathway. Understanding where each of the vitamin K dependent factors function is crucial because it also correlates with the order in which each clotting factor will be depleted. The circulating half-life of factors VII, IX, X, and II are 6, 14, 16, and 40 hours respectively, in dogs. Hemostasis can be impaired one to two days post-consumption of rodenticide.

The toxicosis created by rat bait is characterized by various manifestations of hemorrhage. Clinical signs include epistaxis, hyphema, hematuria, melena, hemothorax, hemoabdomen, hematomas, and anemia. These lead to other clinical signs such as depressed attitude, weakness, ataxia, and sometimes petechiation. Other non-specific signs that have also been reported are swollen joints from hemorrhage into joint capsule, limping, coughing, wheezing, pale mucous membranes and sudden death.

If rodenticide ingestion is suspected and cannot be confirmed, checking circulating clotting factors would be included in initial work-up. Since clotting factor VII is the first factor to be depleted within the first 6 hours post-ingestion, PT should be performed since it tests for abnormalities in the extrinsic pathway. However, if duration is unknown and it has possibly been a few days since rodenticide ingestion then PT, PTT and possible ACT should be performed to test all three pathways. Other basic bloodwork should include a complete blood count to evaluate hematocrit, red blood cell count, white blood cell count, and platelets. The hematocrit will aid in determining the need for a plasma transfusion. Another diagnostic tool that can be used is ultrasound. It can be useful for determining if any free fluid is present in the thoracic cavity or abdomen.

Treatment and Management Options:

Vitamin K dependent clotting factors are the main target of anticoagulants making vitamin K supplementation the cornerstone of treatment. The commonly accepted route of vitamin K administration is subcutaneous. However, it is thought that subcutaneous absorption does not have a reliable absorption rate. It is recommended to administer the high dose to ensure effectiveness. High doses of Vitamin K have caused Heinz body hemolytic anemia in cats, but is generally well tolerated, especially in dogs. Oral doses of Vitamin K can also be administered, but similar to subcutaneous injections, it can be considered unreliable so the high dose is also recommended. Intravenous administration of vitamin K is also an accepted treatment option. There have been reports of anaphylaxis in dogs with intravenous administration, but in a 2013 study involving 73 dogs that evaluated coagulation times after intravenous administration, none had an adverse reaction. The recommended dosing for Vitamin K is 3-5 mg/kg which can be applied to the oral, subcutaneous and intravenous route. The duration of treatment is dependent upon which anticoagulant was consumed. If it is a first generation anticoagulant, then vitamin K supplementation should not exceed more than one week. Consumption of a second generation anticoagulant will require vitamin K supplementation for several weeks. As mentioned earlier, the treatment duration is directly correlated with the anticoagulant tissue persistency.

If a patient presents to the clinic within one hour of ingestion, then the initial treatment is decontamination. Bloodwork can be obtained as a baseline, but the patient should return after 24 hours to recheck bloodwork values or clotting factors. Vitamin K supplementation should be prophylactically given for one week. In severe cases, where the patient is anemic and thrombocytopenic, a plasma transfusion is then indicated. Plasma transfusions are the preferred transfusion product due to its enriched source of clotting factors. Whole blood transfusions are

acceptable, but used primarily in cases where patients are severely hypovolemic or if no plasma is available. Draining a hemothorax, hemoabdomen, or hematomas can also be performed if it is causing complications; however, it is not recommended as the centesis may lead to further hemorrhage. The recommendation is to leave the blood for later resorption. Another treatment that isn't commonly recorded is the use of anti-anxiety medication. In severe cases, anti-anxiety medication can be utilized to keep patients calm and limit activity. Patients that have a tendency to be more active or have an anxious disposition in hospital have a greater risk of having internal hemorrhage which can lead to fatal complications. After several weeks of supplementation, it is recommended that the patient discontinue supplementation for two days then have their coagulation profile and blood work rechecked to ensure there is no residual toxin persisting in the tissues prohibiting clotting factor development.

Case Outcomes:

Blood work results were discussed with the owner and treatment recommendations were made. It was decided to give Luc a plasma transfusion and Beau was started on fluids and vitamin K supplementation. Luc received 240 mls of plasma. He had no adverse reactions to the transfusions. Luc was also started on fluids and vitamin K supplementation along with the transfusion. They were both hospitalized overnight for monitoring. Their clinical signs improved overnight and Luc had another coagulation profile performed the following morning revealing normal values: PT was 8.5 (5.0-12.0) and PTT was 11.4 (10.0-20.0). Due to financial restrictions and their improving/stable condition, both patients were discharged the following day. They both went home on vitamin K supplements and Trazodone. The owner was advised to purchase more vitamin K supplements as both patients would need supplementation for several weeks. On follow-up six weeks later, the owners reported that Beau and Luc were doing well and seemed to

be recovered. They were still administering the vitamin K daily and were going to have the coagulation profile rechecked at their veterinarian to see if supplementation should be continued or discontinued.

Conclusion:

Rodenticide toxicity is an unfortunately common small animal toxicity that manifests in various forms of hemorrhage. The basis of diagnosis involves thorough history, physical exam, as well as bloodwork and coagulation profile. Thorough history can be a differentiating factor to exclude all other clotting disorders. It is important to remember that when obtaining history to find out the active ingredient to determine if it is a first or second generation so that way an effective treatment plan is determined. Treatment for anticoagulant rodenticide toxicity is based on which generation of anticoagulant has been consumed and how long it has been since consumption. Vitamin K supplementation is the cornerstone of treatment and most patients will do well with that alone unless in severe cases and need plasma transfusions. Duration of treatment is based on whether the rodenticide is first or second generation, as second generation has longer tissue persistency and needs several weeks of supplementation. Bloodwork and a coagulation profile should be rechecked two days after discontinuing supplementation to ensure there is no residual toxin prohibiting development of the vitamin K dependent clotting factors.

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