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CASE REPORT

Successful management and recovery of a dog with immune-mediated thrombocytopenia following vincristine overdose

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Abstract

Objective: To describe the management and outcome of a dog following a 10-fold dosing error of vincristine.

Case Summary: A 2-year-old neutered female Toy Fox Terrier presenting for immune-mediated thrombocytopenia was administered an accidental overdose of vincristine (0.2 mg/kg [2.71 mg/m^2]). The dog was managed for severe gastrointestinal signs, neutropenia, and neurological consequences secondary to the overdose. Neurological signs included diffuse muscle tremors, limb hyperextension, and myalgia during the dog's hospitalization. Medical management consisted of aggressive supportive care in addition to novel strategies, including folinic acid, glutamic acid, and Tbo-filgrastim. The dog was discharged from the hospital after 12 days of hospitalization and recovered completely within a month of the overdose with no lasting consequences.

New or Unique Information Provided: This is the first report of the successful management of severe vincristine overdose in a dog. Therapy included the use of Tbo-filgrastim, folinic acid, and glutamic acid along with aggressive supportive care.

KEYWORDS
granulocyte-colony stimulating factor, neurotoxicity, neutropenia, toxicity, vincristine

1 | INTRODUCTION

Chemotherapeutic agents target rapidly dividing cells and have a narrow margin of safety with significant potential side effects, and precise dosing is essential.[1] Vincristine is a vinca alkaloid antimicrotubule chemotherapeutic agent that is commonly utilized as a single agent, or in a multidrug protocol, for many different types of tumors in dogs.[1] In addition to its effect on rapidly dividing cells, vincristine potentially plays a role in thrombopoiesis stimulation, megakaryocyte fragmentation, production of platelet antibodies, platelet destruction, and phagocytosis.[2] These effects have led to its utilization in the treatment of immune-mediated thrombocytopenia (ITP), resulting in a more rapid improvement in platelet count and shorter hospitalization time when implemented with standard therapy for ITP.[2,3] Reported adverse effects in veterinary medicine include gastrointestinal signs, bone marrow suppression, and, rarely, neurological signs, but side effects specific to vincristine for ITP management have not been reported.[1–4]

To our knowledge, this is the first report discussing the management and survival of a dog after acute, severe vincristine toxicity.

Abbreviations: G-CSF, granulocyte colony-stimulating factor; ITP, immune-mediated thrombocytopenia; NG, nasogastric.

2 | CASE SUMMARY

A 2-year-old neutered female Toy Fox Terrier weighing 2.5 kg was presented to the emergency service at a university teaching hospital for further investigation of severe thrombocytopenia of 3 months duration. Medical management with short courses of immunosuppressive agents had been attempted and was unsuccessful. The dog developed petechiation 2 days prior to presentation.

Physical examination revealed a body temperature of 39.1°C (102.5°F), heart rate of 150/min, respiratory rate of 44/min, pink mucous membranes, and a capillary refill time of less than 2 s. Mild petechiation on the dog's ventrum and pinnae were noted. An ECG was performed and was consistent with sinus tachycardia. The dog's systolic blood pressure was slightly increased at 150 mm Hg. As the patient appeared overly anxious and otherwise cardiovascularly stable, acepromazine[a] (10 μg/kg, IV) was administered, in addition to an isotonic crystalloid fluid bolus (lactated Ringer's solution[b]; 24 ml/kg over 5 min) and hydromorphone[c] (0.1 mg/kg, IV), which led to normalization of the dog's heart rate.

A CBC and serum biochemistry profile were performed and demonstrated a severe thrombocytopenia ($3 \times 10^9/\mu$l; reference interval [RI], 200—500 $\times$ $10^9/\mu$l), mild eosinophilia ($1.64 \times 10^3/\mu$l; RI, 0.0–$0.75 \times 10^3/\mu$l), normal HCT (0.42L/L [42.35%]; RI, 0.37–0.55 L/L [37.0%–55.0%]), and an increased creatine kinase activity (352 IU/L; RI, 25—200 IU/L). Urinalysis, prothrombin time, activated partial thromboplastin time, thoracic radiographs, abdominal radiographs, abdominal ultrasound, and echocardiogram were unremarkable. The dog was previously tested for tick-borne diseases with a commercially available ELISA,[d] which was negative. The blood type was dog erythrocyte antigen 1 positive.

The dog was admitted to the hospital for treatment of presumptive primary ITP. Medical management on day 1 of hospitalization included IV fluid therapy, prednisone[e] (2 mg/kg, PO, q 24 h), doxycycline hyclate[f] (5 mg/kg, PO, q 12 h), metoclopramide[g] (2 mg/kg/day, IV), maropitant citrate[h] (1 mg/kg, IV, q 24 h), trazodone[i] (5 mg/kg, PO, as needed), and acepromazine[a] (0.01 mg/kg, IV, as needed). The owner declined extensive vector-borne disease testing, and doxycycline was prescribed empirically. Gastrointestinal medications were prescribed as the patient was reported to have regurgitated prior to presentation. Vincristine[j] was administered on the day of admission (day 1). An error in dose calculation was made, and the dog inadvertently received 10 times the intended dose (0.2 mg/kg, IV, or 2.71 mg/m^2, instead of 0.02 mg/kg, IV). Overnight, the dog regurgitated on multiple occasions and developed hematochezia.

The erroneous dosing was noted 18 h after administration, on day 2 of hospitalization. Examination at that time revealed the dog to be quiet, alert, and responsive with normal vital parameters. The petechiae over the dog's ventrum were more extensive than the previous day. The dog became anorexic, nauseous, continued to regurgitate frequently, and developed severe abdominal pain. In addition to the previously mentioned medical management, intensive supportive care was implemented as per the recommendation of a commercially available animal poison control center[k] and the available literature because

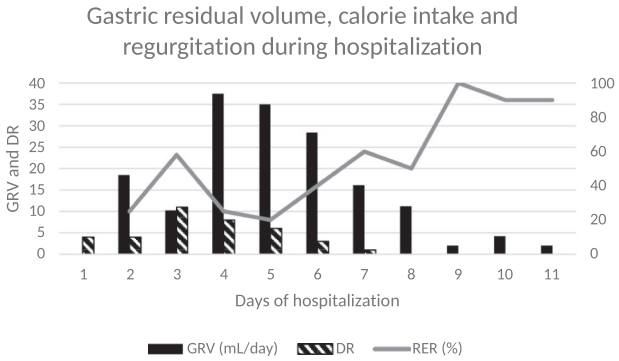

FIGURE 1 Time plot of daily regurgitation (DR), gastric residual volume (GRV) from the nasogastric tube, and calorie intake on resting energy requirement (RER) through hospitalization. Resting energy requirement was calculated based on the equation (30 × weight [kg] + 70) kilocalories

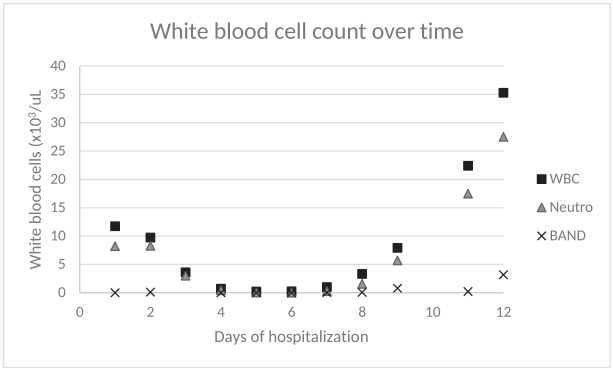

FIGURE 2 Time plot of WBC count throughout hospitalization

severe bone marrow suppression and gastrointestinal adverse effects were expected.[1,9,11–14,18] Therapy consisted of nasogastric (NG) tube placement for assisted enteral nutrition,[l] cholestyramine[m] (0.8 g/kg, NG, q 8 h for 3 days) for further decontamination considering enterohepatic recirculation, ondansetron[n] (0.5 mg/kg, IV, q 12 h), cisapride[o] (1 mg/kg, IV, q 8 h), pantoprazole[p] (1 mg/kg, IV, q 12 h), ampicillin–sulbactam[q] (30 mg/kg, IV, q 8 h) for the impending neutropenia, *n*-acetylcysteine[r] (140 mg/kg, IV, once, followed by 70 mg/kg, IV, q 6 h) for hepatoprotection considering potential hepatotoxicity, Tbo-filgrastim[s] (5 μg/kg, SC, q 12 h on the first day, then q 24 h) to prophylactically promote neutrophil proliferation, and folinic acid[t] (0.3 mg/kg, IV, q 8 h) for its presumed protective effects against vincristine toxicity. The dog's abdominal pain was treated with a continuous infusion of fentanyl[u] (3 μg/kg/h). Oral prednisone[e] and doxycycline[f] were discontinued, and dexamethasone sodium phosphate[v] (0.3 mg/kg, IV, q 24 h) and IV doxycycline[w] (10 mg/kg, IV, q 12 h) were initiated. Every 4 h, gastric residual volume was quantified, and assisted enteral feeding with a commercial elemental diet[l] was administered. Figure 1 demonstrates daily gastric residual volume, regurgitation frequency, and nutritional support provided throughout hospitalization. A jugular venous sampling line was placed to facilitate blood collection and medication administration.

The dog's neutrophil count started to decrease on day 3. Figure 2 shows the dog's WBC count throughout hospitalization. The dog was

noted to be more tachycardic and anemic, with a PCV of 20% and total plasma proteins of 3.6 g/dl. The dog was administered a fresh whole blood transfusion (40 ml/kg over 4 h), which she tolerated well.

On day 4, her neutrophil count decreased from $3 \times 10^3/\mu l$ to $0.42 \times 10^3/\mu l$. Biosafety measures were instituted, including personal protective equipment for all handling of the patient. Melena was also noted, and sucralfate[x] (200 mg, NG, q 6 h) was added to the dog's medical management. The dog was again anemic, quiet, and had a progressive sinus tachycardia. The dog received a stored whole blood transfusion (40 ml/kg, over 4 h) from the same donor and donation as the previous day, which normalized the heart rate and improved the PCV. Later that day, a neurological episode lasting approximately 40 s was noted, during which the dog was laterally recumbent with diffuse muscle tremors and dull mentation. The episode resolved prior to intervention, but the dog remained dull. Evaluation revealed mild hypertension (170 mm Hg), and venous blood gas analysis did not show any significant findings. Considering the concerns for cerebral edema and intracranial hypertension, the dog was given a dose of hypertonic saline[y] (NaCl 7.2%; 5 ml/kg, IV, over 15 min). Within 5 min of the first event, the dog again experienced head tremors. A bolus of midazolam[z] (0.25 mg/kg, IV) was administered, which abolished the head tremors. The dog had 2 additional episodes later that day, each lasting less than a minute. Continued intermittent tremor episodes occurred throughout hospitalization, lasting between 1 and 5 min. The dog's cranial nerve examination, spinal reflexes, and conscious proprioception remained normal.

On day 6, jaw pain, reluctance to open the mouth, and generalized discomfort were noted on physical examination. The dog reached the nadir WBC count on that day, with a neutrophil count of $0.01 \times 10^3/\mu l$. The dog became febrile for the first time on that day, and enrofloxacin[aa] (10 mg/kg, IV, q 24 h) was added to the regimen to broaden the antimicrobial spectrum. The dog started eating after the addition of capromorelin[ab] (3 mg/kg, PO, q 24 h).

Glutamic acid[ac] (100 mg/kg, PO, q 8 h) was started on day 7 of hospitalization as an adjunctive therapy for management of the vincristine-associated neurotoxicity. Gabapentin[ad] (10 mg/kg, PO, q 8 h) was prescribed, and the continuous-rate infusion of fentanyl[u] was tapered and discontinued. The dog's stools were still soft, but the melena had resolved.

On day 8, the patient was quiet, had a persistent fever, and hyperbilirubinemia (32.5 μmol/L [1.9 mg/dl]; RI, 1.7–10.2 [0.1–0.6]) was newly found. Metronidazole[ae] (10 mg/kg, IV, q 12 h) was added empirically to cover for bacterial cholangiohepatitis and provide 4-quadrant antimicrobial coverage, as no other abnormalities were noted on exam, catheter, or bloodwork evaluation. The dog's platelet count was above $40{,}000 \times 10^3/\mu l$ for the first time. The progression of the dog's platelet count throughout her hospitalization is described in Figure 3. A stiff gait with hyperextension of the dog's hind limbs was noted. The conscious proprioception and spinal reflexes were otherwise normal. The dog's abnormal gait persisted throughout the remainder of hospitalization. The episodes of tremors became less frequent.

The dog's resting energy requirement was being met voluntarily by day 9, and the neutrophil count had recovered. The dog's CBC showed a neutrophilic leukocytosis with regenerative left shift for the remainder of hospitalization.

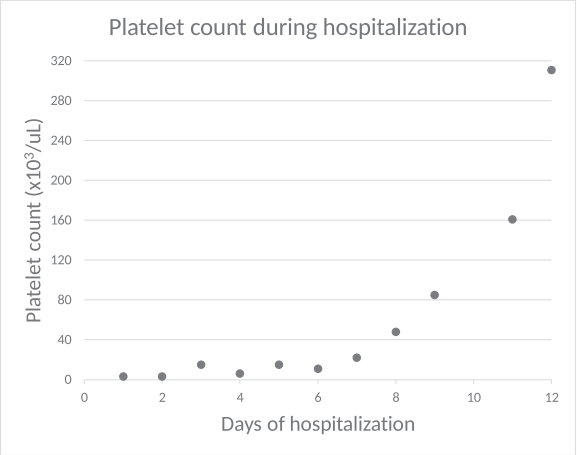

FIGURE 3 Time plot of the platelet count throughout hospitalization

The dog was discharged after 12 days of hospitalization. Episodes of tremoring were occurring 2–3 times a day at the time of discharge. The dog's hind limbs continued to be hyperextended and stiff when walking. The dog was discharged with prednisone[e] (2 mg/kg, PO, q 24 h, until recommended otherwise) for management of ITP, doxycycline hyclate[f] (5 mg/kg, PO, q 12 h, for a total of 4 weeks) for empirical treatment of tick-borne diseases, capromorelin[bb] (3 mg/kg, PO, q 24 h), cisapride[af] (1 mg/kg, PO, q 12 h), metronidazole[ag] (10 mg/kg, PO, q 12 h, until her reevaluation), enrofloxacin[ah] (9 mg/kg, PO, q 24 h, for 3 more days), and glutamic acid[cc] (100 mg/kg, PO, q 8 h).

The dog continued to improve at home and was seen by the primary care veterinarian 1 week after being discharged. Physical exam was unremarkable, and a CBC revealed a thrombocytosis ($537 \times 10^3/\mu l$) and a moderate neutrophilic leukocytosis (WBC $32.13 \times 10^3/\mu l$; neutrophil $27.72 \times 10^3/\mu l$).

The dog was reevaluated at the university teaching hospital 1 month after discharge. All neurological signs had resolved. Medical management at home included prednisone[e] (2 mg/kg, PO, q 24 h) and glutamic acid[cc] (100 mg/kg, PO, q 8 h). The dog's physical examination was unremarkable, and the CBC was within reference range, with resolved band neutrophilia and eosinophilia. The serum biochemistry profile showed a mild increase in alanine aminotransferase activity (87 IU/L; RI, 19–80). Glutamic acid[cc] was discontinued, and the dog's prednisone dose was decreased by 25%.

3 | DISCUSSION

Vincristine administration at chemotherapeutic dosing can be associated with gastrointestinal signs and myelosuppression.[5] Neurological signs have been reported at therapeutic doses but are rare and self-limiting.[6–8] Two reports of severe acute vincristine toxicity

are currently available in the veterinary literature; however, both overdoses were ultimately fatal.[9,10]

The dog in this case report survived the administration of a 10-fold overdose of vincristine. The dog received 0.2 mg/kg (or 2.71 mg/m^2) of vincristine intravenously, whereas the reported dose of vincristine for chemotherapy is 0.5–0.75 mg/m^2.[1] In this case, the overdose was noted 18 h after the administration. Decontamination is a cornerstone of toxicity management. Unfortunately, due to the delay in error identification, and the short half-life and large volume of distribution in dogs, it was determined that plasmapheresis was not likely to be of value.[11] Vincristine is metabolized by the liver, excreted in the bile, and has been detected in the bile up to 2 weeks after administration.[12] Considering the known biliary excretion of the drug, cholestyramine was added to potentially prevent enterohepatic recirculation of the drug. In addition to decontamination measures, interventions in this case were aimed at altering vincristine metabolism and managing the severe bone marrow suppression, refractory gastrointestinal signs, and neurological consequences.

The dog developed a grade IV neutropenia during hospitalization, defined as a neutrophil count below 0.5×10^3/L, beginning on day 3.[1,13] Antimicrobial monotherapy and barrier nursing precautions were initiated immediately. To prevent early bacterial selection, the dog's vital parameters were monitored closely, and the antimicrobial spectrum was not broadened until the patient was noted to be febrile on day 6. Febrile neutropenia occurs more frequently in human oncology, and prophylactic use of granulocyte colony-stimulating factor (G-CSF) to decrease the risk of morbidity and mortality is usually recommended in high-risk patients.[13] The use of G-CSF has been rarely reported in veterinary medicine. Filgrastim, a recombinant human G-CSF, has been investigated in veterinary medicine for different situations, including chemotherapy-induced myelosuppression and bone marrow transplantation.[13,14] Tbo-filgrastim was the only recombinant human G-CSF available and has been shown to be bioequivalent to filgrastim, but its use has not been previously reported in veterinary medicine.[15] An equivalent dose of filgrastim to the Tbo-filgrastim dose prescribed in this case report has been reported to be well-tolerated by dogs.[14]

Vincristine-induced neurotoxicity is the main dose-limiting adverse effect in people.[12,16] It interferes with the axonal microtubules, reducing axonal transport and causing axonal degeneration,[16] and causes a symmetrical sensorimotor polyneuropathy that includes neurogenic pain, paralytic ileus, constipation, bladder atony, and paresthesia.[12,16,17] Agitation, confusion, depression, and psychosis are also known neurological symptoms, which can be associated with direct neurotoxicity or, uncommonly, by hyponatremia from an inappropriate antidiuretic hormone release.[12,16] The neurological signs progressively appear within the first week of administration and usually resolve within 6 weeks after the drug has been discontinued.[16,17] The dog in this case started exhibiting neurological signs on day 4, including altered mentation and diffuse muscle tremors. The dog progressed to having a depressed mentation, jaw pain, and diffuse myalgia, and developed a stiff gait with hyperextended hind limbs. All those changes resolved within a month of the overdose, as has been described in human medicine.[17] Management of neurological signs included the administration of glutamic and folinic acid. Glutamic acid was added to therapy because it has been shown in murine models to improve survival when administered with lethal doses of vincristine; although its mechanisms of action is unknown, an interaction with tubulin has been suggested.[12,18] It has been shown to delay the onset of neurotoxicity and decrease the overall neurotoxicity in human patients.[12,19] In this case, administration was initiated later during the hospitalization due to its limited access. Folinic acid has been suggested to potentially reverse the cytotoxic effects of vincristine by allowing the cells in mitotic arrest to recover their capacity to synthetize RNA, but its efficacy is still to be proven.[9,17,20–22] Considering the lack of data on folinic acid use in dogs, the dose prescribed to the patient in this report was extrapolated from an experimental canine model of pyrimethamine toxicity and human data.[20,23]

Clinical hepatotoxicity is rarely reported with vincristine, but liver necrosis has been noted on postmortem examination in people and a cat.[9,24] The dog in this case report was treated with *n*-acetylcysteine for hepatoprotection because increased glutathione levels have been shown to improve cell viability and resistance to vincristine by improving drug efflux through multidrug resistance protein-1.[25] The dog in this report developed a mild increase in alkaline phosphatase and alanine aminotransferase activities, which improved with time. Chemotherapy-induced gastrointestinal signs are common but, with appropriate use, oncological treatments rarely result in severe adverse events.[13] Chemotherapy agents can cause vomiting, nausea, diarrhea, and ileus from direct irritation and destruction of the rapidly dividing cells of the gastrointestinal tract but also from stimulation of the central nervous system.[13] Vincristine neurotoxicity has also been associated with ileus from its effect on the autonomic nervous system.[16] Considering the significant overdose in this case, the patient was expected to have severe gastrointestinal complications. Early intensive gastrointestinal supportive care and assisted enteral nutrition were initiated immediately. Considering the availability of platelet replacement products at the authors' institution and the benefit of enteral nutrition, an NG tube was placed in face of the potential risks of bleeding. A combination of antinausea, antiemetic, prokinetic, and appetite stimulant medications was used to promote voluntary food consumption. A proton-pump inhibitor and sucralfate were used for the management of esophagitis associated with the dog's frequent regurgitations and upper gastrointestinal bleeding. Different types of diets were offered prior to every feeding to promote voluntary intake. If inappetent or eating fewer than the intended daily calories, nutrition was provided though an NG tube. Gastric residual volumes were measured to evaluate for any evidence of ongoing enteral feeding intolerance. The patient started showing interest in food on day 6 of hospitalization and was voluntarily consuming the resting energy requirement on day 9. The patient experienced frequent episodes of regurgitation during the first 5 days of hospitalization, which subsequently improved. The patient was eating well at home after being discharged but still required to be fed in small meals to prevent regurgitation. At the last reevaluation, the dog was able to tolerate normal-sized meals twice daily without any medical intervention.

Chemotherapeutic agents are frequently used in veterinary medicine and have a narrow margin of safety. Improper use is harmful to the patient but also to the personnel handling the drugs. In this case, a verbal miscommunication led to a decimal-point error and administration of 10 times the intended dose. Following this incident, changes to standard operating procedures were developed, with multiple dose verification and patient checkpoints prior to the administration of drugs with narrow dosing margin, such as vincristine and other chemotherapeutic agents.

This is the first case report of a dog recovering from severe vincristine overdose (0.2 mg/kg, or 2.71 mg/m^2). Although severe gastrointestinal consequences, bone marrow suppression, and neurological signs were displayed, with the aggressive supportive care measures described, the dog recovered with no long-term complications. This case report also describes the utilization of novel therapeutic interventions, including Tbo-filgrastim, glutamic acid, and folinic acid in dogs.

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ENDNOTES

[a] Acepromazine, MWI Animal Health, Boise, ID.
[b] Lactated Ringer's solution, B. Braun Medical Inc, Bethlehem, PA.
[c] Hydromorphone, Hospira Inc, Lake Forest, IL.
[d] Snap4dx, IDEXX Laboratories Inc, Westbrook, ME.
[e] Prednisone, West-Ward, Eatontown, NJ.
[f] Doxycycline, Sun Pharmaceutical Industries Inc, Cranbury, NJ.
[g] Metoclopramide, Hospira Inc, Lake Forest, IL.
[h] Maropitant citrate (Cerenia), Zoetis LLC, Kalamazoo, MI.
[i] Trazodone, Major Pharmaceuticals, Lironia, MI.
[j] Vincristine, Hospira Inc, Lake Forest, IL.
[k] ASPCA Poison Control Center, New York, NY.
[l] Vivonex plus, Nestle Healthscience, Bridgewater, NJ.
[m] Cholestyramine, Zydus Pharmaceuticals, Pennington, NJ.
[n] Ondansetron, Accord Healthcare Inc, Durham, NC.
[o] Cisapride (Compounded), Iowa State University College of Veterinary Medicine, Ames, IA.
[p] Pantoprazole, West-Ward, Eatontown, NJ.
[q] Ampicillin and sulbactam, Auromedics Pharma LLC, E. Windsor, NJ.
[r] N-acetylcysteine (inhalant), Hospira Inc, Lake Forest, IL.
[s] Tbo-filgrastim (GRANIX injection), Teva Pharmaceuticals, North Wales, PA.
[t] Leucovorin calcium injectable, Fresenius Kabi USA LLC, Lake Zurich, IL.
[u] Fentanyl citrate, Hospira Inc, Lake Forest, IL.
[v] Dexamethasone SP, West-Ward, Eatontown, NJ.
[w] Doxycycline, Fresenius, Kabij, Lake Zurich, IL.
[x] Sucralfate, McKesson, Memphis, TN.
[y] NaCl 7.2%, NovaTech Inc, Grand Island, NE.
[z] Midazolam, Hospira Inc, Lake Forest, IL.
[aa] Enrofloxacin (Baytril injectable), Bayer Healthcare LLC, Shawnee Mission, KS.
[ab] Capromelin (Entyce), Aratana Therapeutics Inc, Leawood, KS.
[ac] Glutamic acid, Swanson Health Products, Fargo, ND.
[ad] Gabapentin, Actavis Elizabeth LLC, Elizabeth, NJ.
[ae] Metronidazole, Hospira Inc, Lake Forest, IL.
[af] Cisapride (Compounded), Iowa State University College of Veterinary Medicine, Ames, IA.
[ag] Metronidazole (Compounded), Iowa State University College of Veterinary Medicine, Ames, IA.
[ah] Enrofloxacin (Baytril oral), Bayer Healthcare LLC, Shawnee Mission, KS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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