JOURNAL OF
Veterinary Emergency
AND Critical Care

Case Report

Journal of Veterinary Emergency and Critical Care **28**(4) 2018, pp 356–360
doi: 10.1111/vec.12729

Treatment of carprofen overdose with therapeutic plasma exchange in a dog

Astrid B. Kjaergaard, DVM; Jennifer L. Davis, DVM, PhD, DACVCP and Mark J. Acierno, MBA, DVM, DACVIM

Abstract

Objective – To report the use of therapeutic plasma exchange (TPE) in a dog with carprofen toxicosis.
Summary – A 6-year-old female neutered Bichon Frise weighing 6.9 kg was examined after it had ingested 72 mg/kg carprofen. Mild dehydration without azotemia and with a urine specific gravity of 1.050 was noted at presentation. Treatment consisted of induction of emesis, symptomatic medical therapy, and TPE. The TPE achieved 1.5 plasma volume exchanges over 3 hours. Blood samples and effluent samples were collected every 30 minutes during TPE and additional blood samples were collected 11 and 35 hours after treatment. Carprofen concentrations in these samples were determined by high-pressure liquid chromatography. A 51% reduction in serum carprofen concentration was achieved following TPE.
New or Unique Information Provided – This report describes the successful reduction of plasma carprofen concentration in a dog using TPE. Although recent studies suggest that this particular dog may not have received a toxic dose, a 51% reduction of plasma carprofen concentration was achieved over 180 minutes, and TPE may be beneficial for treatment of dogs that have ingested higher doses.

(J Vet Emerg Crit Care 2018; 28(4): 356–360) doi: 10.1111/vec.12729

Keywords: canine, kidney injury, NSAID toxicity, plasmapheresis

Abbreviations

HPLC	high-performance liquid chromatography
NSAID	nonsteroidal anti-inflammatory drug
TPE	therapeutic plasma exchange

Introduction

Carprofen is the most commonly prescribed nonsteroidal anti-inflammatory drug (NSAID) for dogs.[1] It reversibly decreases conversion of arachidonic acid to prostanoids through inhibition of the cyclooxygenase-1 and cyclooxygenase-2 enzyme systems, and thus has both anti-inflammatory and analgesic properties.[2] In the United States, carprofen is labeled for control of pain and inflammation in dogs associated with osteoarthritis, and for alleviation of pain following surgery.[3] Flavored chewable tablets are commercially available, which may increase the risk of accidental ingestion.

Carprofen is a racemic mixture containing equal amounts of 2 enantiomers.[4,5] In dogs, both enantiomers have excellent oral bioavailability, and peak plasma concentrations occur within 1 to 3 hours after oral ingestion.[6] More than 99% of the drug is bound to plasma protein, resulting in a small volume of distribution (V_d, 0.18 L/kg).[7] Elimination half-life in the dog ranges from 8 to 18 hours.[7] The majority of ingested carprofen is metabolized by hepatic conjugation to an ester glucuronide, which is then eliminated in the feces.[3,8] Approximately 34% of the excreted carprofen is resorbed from the gastrointestinal tract and reenters circulation,[5] prolonging the half-life.

NSAID exposure is one of the most common reasons for pet owners to contact veterinary toxicology help lines.[9–11] The symptoms of NSAID toxicosis are attributed to inhibition of the cytoprotective effects of prostaglandins in the gastrointestinal tract and the renal, hemostatic, reproductive, and central nervous systems.[2] Any condition resulting in dehydration can increase the risk of kidney injury caused by NSAID administration.[12] Enterohepatic recycling may contribute to toxicity by

From the Section of Companion Animal Medicine, Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803 (Kjaergaard, Acierno); and the Large Animal Analysis Laboratory, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27613 (Davis).

The authors declare no conflict of interests.

Address correspondence and reprint requests to
Dr. Mark J. Acierno, Midwestern University - Companion Animal Clinic, 19555 N 59th Ave, Glendale, AZ 85308.
Email: macier@midwestern.edu
Submitted March 31, 2016; Accepted September 11, 2016.

© Veterinary Emergency and Critical Care Society 2018

extending the duration of increased plasma concentrations. The literature has suggested that exposure to carprofen at oral doses of 20–30 mg/kg can result in severe gastrointestinal upset while exposure to 30–40 mg/kg can result in acute kidney injury,[12,13] but in a recent study, acute kidney injury failed to materilize when a single oral dose of 120 mg/kg of carprofen was administered to 8 dogs.[14]

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification modality in which pathologic substances, such as toxins, immune complexes, and autoantibodies are removed by extracting the patient's plasma and replacing it with another physiologically compatible solution. Filtration-based TPE may be performed with most continuous renal replacement units. In this form of TPE, the patient's blood is exposed to a positive transmembrane pressure that causes ultrafiltrate (plasma) to be forced out of the semipermeable membranes of the dialyzer. This plasma is discarded, while the cellular components are mixed with a colloid solution and returned to the patient.[15] This allows for relatively efficient removal of proteins and protein-bound substances. In human medicine, TPE has been used to treat a number of autoimmune diseases, as well as some intoxications.[16] Successful use of TPE has been reported in patients with immune-mediated hemolytic anemia[17] and multiple myeloma with hyperviscosity syndrome.[18] No complications were noted when TPE was performed in dogs weighing <14 kg.[19] The role of TPE for treatment of canine intoxications has yet to be fully investigated; however, the authors have previously used TPE to treat both ibuprofen and meloxicam intoxications.

Historically, treatment of carprofen intoxication in the dog has been limited to decontamination using emesis and activated charcoal, intravenous fluids, and the administration of antiemetics, gastrointestinal protectants, and prostaglandin analogs.[10] This report describes the adjunctive treatment of carprofen intoxication in a dog using TPE.

Case Report

A 6-year-old 6.9 kg female neutered Bichon Frise presented to our facility 2 hours after it was discovered to have ingested 500 mg of carprofen[a] (72 mg/kg). The actual time of the ingestion was unknown and could have ranged from 2 to 6 hours prior to presentation. The dog's primary care veterinarian had induced vomiting using apomorphine infused into the conjunctival sac (dose unknown). No remnants of the carprofen were observed in the vomitus and the patient was referred for additional care.

Upon presentation to our facility, the dog was bright, alert, and responsive. Rectal temperature, heart rate, respiration rate, and systemic arterial blood pressure were within institutional reference intervals. The physical examination of the dog was unremarkable other than an estimated 5% dehydration. Blood was collected for a CBC and serum biochemical profile. The results of the CBC revealed leukopenia with a normal cellular differential. The results of the serum biochemistry analysis indicated hypoglobulinemia, a hyperchloremic metabolic acidosis, and hypokalemia (Table 1). The serum creatinine concentration was within the institutional reference interval (68.6 μmol/L; reference interval 44.2–123.7 μmol/L [0.9 mg/dL, reference interval 0.5–1.4 mg/dL]). The results of a urinalysis were also within the institutional reference intervals for all parameters. An IV bolus (10 mL/kg) of isotonic crystalloid fluid[b] was given, and subsequent crystalloid fluid therapy[b] was initiated at 2.6 mL/kg/h. The crystalloid fluids used for subsequent fluid therapy were supplemented with 28 mmol/L [mEq/L] of KCl.[c] Due to the acute nature of the intoxication and the possible morbidity associated with ingestion of 72 mg/kg of carprofen, a decision was made to perform TPE in conjunction with supportive medical therapy. An additional IV crystalloid fluid bolus (10 mL/kg) was given immediately before the initiation of TPE.

An 8-Fr, 16-cm double lumen temporary dialysis catheter[d] was inserted into the dog's right external jugular vein. A urinary catheter was also placed so that urine output could be monitored, and IV fluids adjusted accordingly. TPE was initiated utilizing an automated system.[e] A disposable extracorporeal circuit incorporating a polypropylene hollow fiber TPE filter with an effective albumin sieving coefficient of 0.97 was selected.[f] The system was primed with 4 L of 0.9% saline with 5,000 U/L of added heparin.[g] Heparin-containing fluids were then rinsed from the unit.

The dog was anticoagulated with an IV bolus of unfractionated heparin (25 U/kg) followed by a continuous rate infusion (20 U/kg/h, IV). Activated clotting times were measured using an automated coagulation timer system[h] prior to initiation of therapy and every 30 minutes thereafter. Adjustments were made in the heparin infusion rate in order to maintain a targeted degree of anticoagulation. TPE was performed for 180 minutes. Systemic arterial blood pressure, electrocardiography, urine output, and vital signs (heart rate, respiratory rate, capillary refill time, and rectal temperature) were monitored throughout the procedure. Blood flow through the extracorporeal circuit was maintained at 100 mL/min with a replacement fluid rate of 90 mL/h; thus, approximately 1.5 plasma volumes (270 mL) were exchanged. A 3% hetastarch[i] mixture (50% hetastarch solution and 50% saline) was utilized as the replacement fluid.

© Veterinary Emergency and Critical Care Society 2018, doi: 10.1111/vec.12729

Table 1: Abnormal serum biochemical activities or concentrations in a dog that ingested a toxic dose of carprofen treated with total plasma exchange

	Day 1	Day 2	Day 3	Reference interval
AST (U/L)	30	183	68	2–38
CK (U/L)	107	N/A	523	67–200
Total plasma protein (g/L)	59	47	50	54–70
[g/dL]	5.9	4.7	5.0	5.4–7.0
Albumin (g/L)	29.0	23.0	24.0	26.0–34.0
[g/dL]	2.9	2.3	2.4	2.6–3.4
Globulin (g/L)	30.0	24.0	26.0	31.0–45.0
[g/dL]	3.0	2.4	2.6	3.1–4.5
Potassium (mmol/L)	3.8	3.5	4.5	4.0–4.6
[mEq/L]	3.8	3.5	4.5	4.0–4.6
Chloride (mmol/L)	123	122	121	114–118
[mEq/L]	123	122	121	114–118

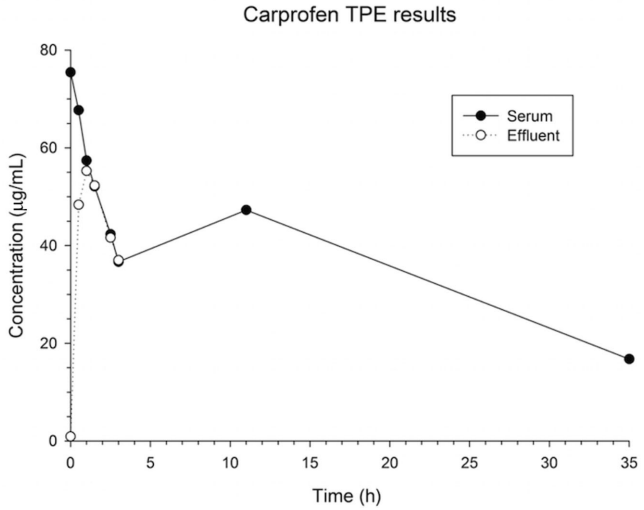

Figure 1: Concentration of carprofen in serum and effluent from a dog treated with total plasma exchange (TPE) after ingestion of 72 mg/kg of carprofen. Exchanges were carried out from 0–3 hours, and additional serum carprofen concentration measurement was performed at 11 and 35 hours after initiation of TPE.

Heparinized blood (2 mL) and effluent (1 mL) samples were collected at 0, 0.5, 1.0, 1.5, 2.5, 3, 11, and 35 hours after initiation of therapy. The blood samples were centrifuged[j] at 500 × *g* for 5 minutes. Serum was then harvested and pipetted into sterile polypropylene cryo-tubes.[k] Samples were frozen and stored at –80°C for future analysis.

Following TPE, 10 mL/kg of fresh frozen plasma was administered IV to replace coagulation factors. A periocular swelling on both eyes and lips as well as some regurgitation was noted during plasma administration, and diphenhydramine[l] was administered (2.2 mg/kg IM, once). Swelling and regurgitation abated, and the plasma administration continued at a slower rate.

Urine output, systemic arterial blood pressure, and coagulation function (prothrombin time and activated partial thromboplastin time) were monitored. Maropitant[m] (1 mg/kg SC), misoprostol[n] (5 μg/kg PO, q 8 h), and pantoprazole[o] (1 mg/kg, IV, q 24h) were administered. Once dehydration was corrected, the rate of isotonic crystalloid fluid administration was adjusted to account for urine production and insensible losses.

On Day 2, regurgitation and periocular swelling had resolved. The patient's physical examination was normal and her appetite was excellent. A serum biochemistry profile revealed panhypoproteinemia (Table 1), which was attributed to the TPE procedure. The hyperchloremic metabolic acidosis and hypokalemia persisted and the dog remained nonazotemic with a serum creatinine concentration of 61 μmol/L (0.8 mg/dL). Urine output monitoring and crystalloid fluid administration were continued for an additional 24 hours. At that time, a serum biochemistry profile revealed improvement in all abnormalities. The serum creatinine concentration was

© Veterinary Emergency and Critical Care Society 2018, doi: 10.1111/vec.12729

68.6 μmol/L (0.9 mg/dL). Forty-eight hours after presentation, the patient was discharged with instructions to administer misoprostol (25 μg PO, q 8 h), sucralfate[p] (200 mg PO, q 8h), and omeprazole[q] (10 mg PO, q 24h). Recheck physical examination and serum biochemistry profile performed 7 days and 1 year after initial presentation were normal.

The plasma and effluent samples collected during the TPE procedure were shipped frozen to a veterinary diagnostic laboratory[r] where concentrations of carprofen were determined in both the serum and effluent by high pressure liquid chromatography (HPLC) with ultraviolet detection at 240 nm. Briefly, samples were extracted using solid phase extraction cartridges[s] conditioned with 1 mL of methanol and water. Next, 0.1 mL of sample combined with 0.1 mL of 4% phosphoric acid in water was extracted and washed with methanol and water (95:5 v/v). The final step was elution with 1 mL of methanol. The eluate was evaporated for 30 minutes at 40°C under compressed nitrogen and reconstituted with 0.25 mL of mobile phase, then transferred to an HPLC injection vial and vortexed for 30 seconds. The mobile phase was a mixture of acetonitrile (50%) and potassium phosphate buffer, pH 3.0 (50%) and was run using an isocratic method at 1 mL/min. A 5 μL aliquot was injected onto the HPLC and separated using a C18 column/guard column.[t] Serum standards were spiked with carprofen reference standard to final concentrations of 0.5–400 μg/mL. Unknown concentrations in serum and effluent samples were then calculated based on the slope of the linear regression of the standard curve. Curves were considered acceptable if the coefficient of determination (R^2) was greater than 0.99 and all standard samples calculated within 15% of the expected concentration.

Prior to the start of TPE, plasma concentration of carprofen in this patient was 75.47 μg/mL, which was more than twice the the C_{max} of 35.3 μg/mL typically achieved in dogs receiving therapeutic doses of 4 mg/kg.[20] A 51% reduction in plasma carprofen concentration was achieved during the 3-hour TPE treatment (Figure 1). Although this reduction was clinically significant, the patient's plasma concentration remained above the therapeutic range.

Discussion

TPE has the ability to remove drugs and toxins that are highly protein bound (>80%) and have a small V_d (V_d < 0.2 L/kg). Carprofen has high protein binding (>99%), low V_d (0.18L/kg),[20] and long plasma half-life,[7,20] supporting the use of TPE for treatment of carprofen intoxication. The amount of a substance that can be removed by TPE is limited because as patient plasma is removed, it is continuously being exchanged for a replacement solution, continuously diluting the remaining substance. Therefore, while a 1.5 plasma volume exchange should result in a 60–70% reduction in any highly protein bound molecule with small V_d, further exchanges become increasingly less efficient. It is for this reason that current recommendations suggest that TPE be limited to 1.5 plasma volume exchanges.[15]

Another reason that the explanation 60–70% reduction in plasma concentration was not seen may have been enterohepatic circulation. Carprofen is metabolized in the liver by conjugation to an ester glucuronide of which 70–80% is then eliminated in the feces.[3,8] An estimated 34% of the ingested carprofen then undergoes enteroheptic recirculation.[5] It is for this reason that repeated doses of activated charcoal have been recommended for the treatment of carprofen overdose[13]; however, a recent study did not describe a benefit of multiple doses of activated charcoal.[14] For this reason, activated charcoal was not administered to the dog reported here. Resorption from the gastrointestinal tract likely explains the less-than-expected decrease in plasma carprofen concentration as well as the rebound peak seen 11 hours following treatment.

Another possible explanation for the observed reduction in plasma carporfen concentration following TPE is that the ingested dose may have led to complete saturation of the available plasma protein binding sites. In this situation, unbound drug may distribute into the tissues, increasing the V_d, and decreasing the effectiveness of the TPE therapy. Unfortunately, no information is available about the V_d of carprofen at supraphysiologic doses.

Any number of fluids could be used as a TPE replacement solution including plasma, albumin, and synthetic colloids[21]; however, in human studies, use of fresh frozen plasma has been associated with increased morbidity and mortality.[22] In addition, since two-thirds of the replacement fluid administered at the beginning of a TPE session will be removed by the end,[15] using plasma as a replacement solution is costly. In people, the most commonly utilized replacement solution is 4–5% human albumin diluted in saline[15]; however, use of human albumin in dogs has been associated with morbidity and mortality.[23] Canine albumin was unavailable at the time of this report. Therefore, we used a 3% hetastarch solution. While use of hetastarch has raised concerns about kidney injury in people, there are no prospective studies that demonstrate if these concerns apply to dogs.[24]

For this dog, TPE was chosen for adjunctive treatment of carprofen toxicosis on the basis that the dose ingested was greater than that thought to cause AKI. Medical management alone was an option; however, the total cost of TPE at our facility (800 USD) is less than the cost of 48 hours of treatment for AKI in our ICU. As a result, we considered TPE to be a reasonable treatment option. With

newer toxicity information available, TPE would likely be considered unnecessary. Hemoperfusion is another extracorporeal blood purification modality that could be considered to treat animals with carprofen intoxication.[25]

TPE is an important adjunct treatment for animals with acute toxicoses where the toxin has both a low V_d and is highly protein bound. The patient in this case experienced a 51% reduction in plasma concentration of carprofen after 1.5 plasma volume exchanges, which took a total of 3 hours. Thirty-two hours after the TPE treatment, the plasma carprofen concentration had decreased an additional 55%. This demonstrates the effectiveness of TPE for reducing plasma concentrations of carprofen.

Footnotes

[a] Rimadyl, Zoetis, Florham Park, NJ.
[b] Plasmalyte A, Baxter Healthcare, Deerfield, IL.
[c] Potassium Chloride for injection USP, Braun, Irvine, CA.
[d] Mila International, Erlanger, KY.
[e] Prismaflex System GAMBRO DASCO S.p.A., Medolla, Italy.
[f] GAMBRO TPE 2000 SET, Gambro Industries, Meyzieu, France.
[g] Heparin sodium injection USP, Sagent pharmaceuticals, Schaumburg, IL.
[h] Medtronic ACT II Coagulation Timer: Medtronic inc., Minneapolis, MN.
[i] 6% Hetastarch in 0.9% NaCl, Hospira, inc., Lake Forest, IL.
[j] LW Scientific, Inc. LWS M24 Combo Microhematocrit Combo Centrifuge, Atlanta, GA.
[k] T309-2A, 2 ml Cryovial, Simport, Beloeil QC, Canada.
[l] Diphenhydramine hydrochloride injection USP, West-Ward Pharmaceuticals, Eatontown, NJ.
[m] Cerenia, Zoetis.
[n] Misoprostol (Greenstone™), Greenstone Ltd, Peapack, NJ.
[o] PROTONIX I.V., Wyeth pharmaceuticals inc., Konstanz, Germany.
[p] Sucralfate tablets USP, TEVA, North Wales, PA.
[q] Prilosec^T Procter & Gamble, Cincinnati, OH.
[r] Large Animal Analysis Laboratory, College of Veterinary Medicine, North Carolina State University, Raleigh, NC.
[s] Oasis HLB, 1cc/30mg, Waters Corporation, Milford, MA.
[t] Agilent Eclipse XDB-C18, 4.6 mm X 150 mm, Agilent Technologies, Santa Clara, CA.

References

1. Hunt JR, Knowles TG, Lascelles BD, et al. Prescription of perioperative analgesics by UK small animal veterinary surgeons in 2013. Vet Rec 2015; 176(19):493–493.
2. Brune K, Furst DE. Combining enzyme specificity and tissue selectivity of cyclooxygenase inhibitors: towards better tolerability? Rheumatology 2007; 46(6):911–919.
3. NADA #141-111 Rimadyl FDA approval. 2013.
4. Lees P, Landoni MF, Ciraudel J, et al. Pharmacodynamics and pharmacokinetics of nonsteroidal anti-inflammatory drugs in species of veterinary interest. J Vet Pharmacol Ther 2004; 27(6):479–490.
5. Priymenko N. Enantioselectivity of the enterohepatic recycling of carprofen in the dog. Drug Metab Dispos 1998; 26(2):170–176.
6. Schmitt M, Guentert TW. Biopharmaceutical evaluation of carprofen following single intravenous, oral, and rectal doses in dogs. Biopharm Drug Dispos 1990; 11(7):585–594.
7. McKellar Q, Pearson T, Bogan JA, et al. Pharmacokinetics, tolerance and serum thromboxane inhibition of carprofen in the dog. J Small Anim Pract 1990; 31(9):443–448.
8. Rubio F, Seawall S, Pocelinko R, et al. Metabolism of carprofen, a nonsteroid anti-inflammatory agent, in rats, dogs, and humans. J Pharm Sci 1980; 69(11):1245–1253.
9. Khan SA, McLean MK. Toxicology of frequently encountered nonsteroidal anti-inflammatory drugs in dogs and cats. Vet Clin North Am Small Anim Pract 2012; 42(2):289–306.
10. Talcott PA, Gwaltney-Brant SM. Nonsteroidal antiinflammatories. In: Peterson M, Talcott P. eds. Small Animal Toxicology, Philadelphia: Elsevier Saunders; pp. 687–708.
11. Caloni F, Cortinovis C, Pizzo F, et al Epidemiological study (2006–2012) on the poisoning of small animals by human and veterinary drugs. Vet Rec 2014; 174(9):222.
12. Volmer P, Mensching D. Risk factors for carprofen toxicosis. Toxicology Brief 2009. Managing acute carprofen toxicosis in dogs and cats. Available at: http://veterinarymedicine.dvm360.com/vetmed/ArticleStandard/Article/detail/608397. Accessed June 3, 2018.
13. Volmer P, Mensching D. Managing acute carprofen toxicosis in dogs and cats. Vet Med 2009; 104(7):325–333.
14. Koenigshof AM, Beal MW, Poppenga RH, et al. Effect of sorbitol, single, and multidose activated charcoal administration on carprofen absorption following experimental overdose in dogs. J Vet Emerg Crit Care 2015; 25(5):606–610.
15. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. Hematology Am Soc Hematol Educ Program 2012; 2012:7–12. https://doi.org/10.1182/asheducation-2012.1.7.
16. Schutt RC, Ronco C, Rosner MH. The role of therapeutic plasma exchange in poisonings and intoxications. Semin Dial 2012; 25(2):201–206.
17. Crump KL, Seshadri R. Use of therapeutic plasmapheresis in a case of canine immune-mediated hemolytic anemia. J Vet Emerg Crit Care 2009; 19(4):375–380 (2009).
18. Lippi I, Perondi F, Ross SJ, et al. Double filtration plasmapheresis in a dog with multiple myeloma and hyperviscosity syndrome. Open Vet J 2015; 5(2):108–12.
19. Posner LP, Willcox JL, Suter SE. Apheresis in three dogs weighing <14 kg. Vet Anaesth Analg 2013; 40(4):403–409.
20. American Academy of Veterinary Pharmacology and Therapeutics. *Carprofen (Veterinary — Systemic). in The United State Pharmacopeial Convention 2007; 1–9*.
21. Kaplan AA. Therapeutic plasma exchange: core curriculum 2008. Am J Kidney Dis 2008; 52(6):1180–1196.
22. Mokrzycki MH, Kaplan AA. Therapeutic plasma exchange: complications and management. Am J Kidney Dis 1994; 23(6):817–827.
23. Cohn LA, Kerl ME, Lenox CE, et al. Response of healthy dogs to infusions of human serum albumin. Am J Vet Res 2007; 68(6):657–663.
24. Glover PA, Rudloff E, Kirby R. Hydroxyethyl starch: a review of pharmacokinetics, pharmacodynamics, current products, and potential clinical risks, benefits, and use. J Vet Emerg Crit Care 2014; 24(6):642–661.
25. Shalkham AS, Kirrane BM, Hoffman RS, et al. The availability and use of charcoal hemoperfusion in the treatment of poisoned patients. Am J Kidney Dis 2006; 48(2):239–241.

© Veterinary Emergency and Critical Care Society 2018, doi: 10.1111/vec.12729