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CASE REPORT

Successful management of severe carprofen toxicity with manual therapeutic plasma exchange in a dog

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Abstract

Objective: To report the use of manual therapeutic plasma exchange (TPE) in a dog with severe carprofen toxicity.

Summary: A 12-year-old neutered female Pembroke Welsh Corgi weighing 20 kg was evaluated after ingesting 223 mg/kg of carprofen. Emesis was attempted with apomorphine at the primary care veterinarian but was unsuccessful, and a dose of activated charcoal with sorbitol was administered. On presentation to the referral center, approximately 8 hours after ingestion, the dog's physical examination revealed mild abdominal discomfort but was otherwise unremarkable. Treatment consisted of a combination of supportive care including activated charcoal with sorbitol, cholestyramine, IV lipid emulsion, and manual TPE. Blood samples were collected prior to the initiation of manual TPE and at the completion of 12 exchange cycles. Carprofen levels were determined by high-pressure liquid chromatography. A 57% decrease in carprofen levels was achieved with the combination of activated charcoal, cholestyramine, IV lipid emulsion, and manual TPE. The dog did not develop organ dysfunction secondary to toxicity and was discharged 4 days after ingestion.

New or Unique Information Provided: This report describes the successful decrease of plasma carprofen in a dog with the combination of decontamination techniques and manual TPE. While TPE has been previously reported as a successful therapeutic in dogs with nonsteroidal anti-inflammatory toxicity, including carprofen, equipment and expertise of this platform is not readily available. Manual TPE is technically simple and can be performed in any hospital with a large blood centrifuge.

KEYWORDS
carprofen, extracorporeal therapy, nonsteroidal anti-inflammatory toxicity, plasma exchange

1 | INTRODUCTION

Carprofen[a] is a commonly utilized nonsteroidal anti-inflammatory medication (NSAID) that is prescribed for a variety of conditions, including osteoarthritis and postoperative pain control.[1] The mechanism of action of carprofen is inhibition of cyclo-oxygenase (COX) activity, which mediates prostaglandin synthesis in states of inflammation.[2] Constitutive COX-1 is responsible for the synthesis of essential physiological gastrointestinal and renal prostaglandins, while inducible COX-2 generates inflammation-mediated prostaglandins.[3] The specificity of COX enzyme inhibition varies by species and NSAID, with carprofen demonstrating selective inhibition of COX-2 in dogs.[4] Carprofen has extremely high oral bioavailability and is rapidly absorbed, with peak plasma concentrations achieved between 1 and 3 hours after oral administration.[5] Carprofen is highly protein bound at 99%, with a low volume of distribution.[6,7] Carprofen toxicity can result in a variety of clinical signs including gastrointestinal, hematological, hepatic, renal, neurological, and systemic abnormalities.[8] Gastrointestinal signs may be seen at doses >20 mg/kg, and acute kidney injury may be seen at doses >40 mg/kg.[8] Hepatic damage is often idiosyncratic and may occur at any dose. Neurological signs have been documented in toxicity at doses ≥281 mg/kg.[8] While the toxic ranges for carprofen are variable, doses up to 160 mg/kg have resulted in minimal complications, including gastrointestinal signs.[9]

Treatment of acute carprofen overdose includes decontamination, gastrointestinal protection, renal support, and symptomatic therapy. In addition to these therapies, hemoperfusion, in combination with hemodialysis and therapeutic plasma exchange (TPE), has been documented as an effective therapy in the treatment of carprofen overdose.[11,12] Extracorporeal techniques, including combination hemoperfusion with hemodialysis and TPE, resulted in decreases of plasma carprofen of 67% and 51%, respectively.[11,12] TPE is a successful modality in the treatment of highly protein-bound toxins and most commonly utilizes a continuous renal replacement unit in which patient blood is exposed to a transmembrane pressure or centrifugation, resulting in plasma removal.[13] Plasma removal allows for removal of proteins and protein-bound substances, such as carprofen.[13] This report describes the use of manual TPE as an adjunctive treatment in a dog with acute, severe carprofen overdose.

2 | CASE REPORT

A 12-year-old neutered female Pembroke Welsh Corgi was presented to Iowa State University 8 hours after ingesting 4463 mg of carprofen[a] (223 mg/kg). The dog had recently been prescribed carprofen[a] for suspected osteoarthritis and had received a 37.5-mg dose orally the night prior to presentation. In the morning of presentation, the dog consumed the remainder of the bottle. The dog presented to the family veterinarian after ingestion, and emesis was attempted with 2 doses of apomorphine[b] (0.04 mg/kg, IV), which was unsuccessful. The dog was given 250 ml (1.2 g/kg) of activated charcoal with sorbitol[c] orally, a dose of maropitant[d] (1 mg/kg, IV), and 90 ml of a balanced isotonic crystalloid. Baseline blood work, including a CBC and biochemistry, was performed. The results of the CBC were unremarkable, with an HCT of 45.7% (reference interval, 37.3%–61.7%). The results of the serum biochemistry were unremarkable, with a baseline creatinine of 1.2 mg/dl (reference interval, 0.5–1.5 mg/dl) (Table 1). The dog was then referred for additional care.

Upon presentation, the dog's vital parameters, including temperature, heart rate, and respiratory rate, were unremarkable. Physical examination revealed mild discomfort on abdominal palpation, but the remainder of the physical exam was unremarkable. An IV bolus of 400 ml of a balanced isotonic crystalloid was given. Intralipid emulsion[e] was initiated at a bolus of 1.5 ml/kg (30 ml, IV) and a constant rate infusion at 0.4 ml/kg/min (470 ml over an hour). Due to the severity of toxicity, the decision to perform manual TPE was made. The patient was sedated with butorphanol[f] (0.2 mg/kg, IV) and dexmedetomidine[g] (2.5 μg/kg, IV), and a 5.5-Fr 13-cm triple-lumen central line was placed in the right jugular vein, with positioning in the cranial vena cava confirmed via thoracic radiographs. An 8-Fr Mila nasogastric (NG) tube was placed into the right nostril, and termination of the tube in the stomach was confirmed via thoracic radiographs. Blood typing determined the patient was dog erythrocyte antigen 1.1 negative. The dog's plasma volume was calculated with the equation: 0.08 × kg × (1 − HCT) = 0.868 L, or 868 ml. The dog underwent 12 cycles of manual TPE totaling 1.5 plasma volumes. This 1.5 plasma volumes was chosen based on previous pharmacokinetic calculations of solute removal describing substance removal to be 63% at 1 plasma volume and 78% at 1.5 plasma volumes in any protein-bound molecule with a small volume of distribution.[14,15] Further exchanges, >1.5 plasma volumes, become increasingly inefficient; therefore, 1.5 plasma volumes was chosen in this case.[14,15] The total volume to be exchanged with 1.5 plasma volumes equaled 1.30 L or 1300 ml. In order to calculate the volume of whole blood to be exchanged, the equation: total plasma volume/(1 − HCT) was used, totaling a whole blood volume of 2.4 L or 2400 ml. Based on the dog's weight of 20 kg, removing 13% blood volume during each exchange necessitated 12 exchanges. To perform each exchange, 212 ml of blood was removed via the central catheter. Four 60-ml syringes were utilized with 7 ml of anticoagulant citrate dextrose solution (ACD)[h] in each syringe (totaling a ratio of ACD:whole blood of 1:7.5). The 240 ml of whole blood and ACD was infused into an empty blood bag. The blood bag was then centrifuged at 3400 × *g* for 17 min at 10°C. Once centrifugation was completed, the plasma was removed and discarded. RBCs were reconstituted in 60 ml of 0.9% sodium chloride[i] and given back to the patient. This entire process was repeated for 12 cycles. The dog's plasma volume was replaced with 1100 ml of dog erythrocyte antigen-negative fresh frozen plasma, 615 ml of synthetic colloid,[j] and 720 ml of 0.9% NaCl.[k] The entire process took approximately 8 hours to complete. Fluid replacement in this case consisted of a combination of fresh frozen plasma, synthetic colloid, and isotonic crystalloids, similar to previously reported replacement protocols in veterinary membrane-based TPE including 35%–65% fresh frozen plasma, 10%–30% human albumin, 0%–10% synthetic colloids, and 0%–50% saline, adjusted based on individual needs.[16] The use of human

TABLE 1 CBC and biochemistry results

	Day 1	Day 2	Day 3	Day 5	Day 12	Reference interval
Hematocrit (%)	45.7	35.8	33.4	37	46.4	37.3–61.7
BUN (mg/dl)	12	2	5	3	5	10–30
Creatinine (mg/dl)	1.2	0.5	0.6	0.7	0.9	0.5–1.5
Total protein (g/dl)	6.9	5.0	5.6	6.0	7.0	5.2–7.1
Albumin (g/dl)	3.0	2.5	2.7	2.8	3.0	2.7–4.0
ALT (U/L)	28	46	52	37	35	19–80
ALP (U/L)	53	116	117	95	52	20–150
Na (mmol/L)	158	148	141	144	157	141–151
K (mmol/L)	4.2	4.1	5.1	3.8	4.8	3.9–5.3

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase.

albumin was deemed unnecessary based on the dog's clinical status. The replacement fluids were administered as a constant infusion throughout all exchanges. Fresh frozen plasma (1100 ml) and synthetic colloids (615 ml) were administered over the course of the dog's 8-hour exchange as a constant rate infusion. Isotonic saline administration was performed via 60-ml reconstitution of the patient's RBCs and replaced rapidly after each cycle. The post- exchange plasma carprofen level sample was obtained immediately after the completion of the 12th cycle. Throughout the process, temperature, heart rate, ECG rhythm, respiratory rate and effort, and systemic arterial pressure were monitored. The dog was maintained on a constant fluid rate of 50 ml/h (60 ml/kg/day) of 0.45% NaCl[k] with metoclopramide[l] (2 mg/kg/day) and 80 mEq/L KCl (0.2 mEq/kg/h). Approximately 3 hours into the manual plasma exchange, the dog developed severe hematochezia. Shortly after the large volume of hematochezia, the dog was noted to be hypothermic at 36.1°C, tachycardic at 180/min, hypotensive with a systolic reading of 40 mm Hg, and hyperlactatemic at 3.38 mmol/L. The dog was resuscitated with balanced isotonic crystalloid solution (20 ml/kg), 7.5% hypertonic saline (5 ml/kg),[m] and active warming. The dog responded to resuscitation, with no other complications or concerns noted throughout the remainder of the manual TPE. A venous blood gas was performed after the 6th cycle, revealing a mild ionized hypocalcemia (0.97 mmol/L, reference interval, 1.24–1.45). The dog was given 10% calcium gluconate (0.5 ml/kg) and magnesium sulfate (0.3 mEq/kg, IV). Additional treatments included pantoprazole[n] (1 mg/kg, IV, q 12 h), misoprostol[o] (50 μg, NG, q 12 h), maropitant[g] (1 mg/kg, IV, q 24 h), cholestyramine[d] (21 g, NG, q 6 h, for 8 treatments), N-acetylcysteine[p] (140 mg/kg bolus followed by 70 mg/kg, IV, q 6 h, for 6 treatments), metronidazole[q] (250 mg, PO, q 12 h), ampicillin–sulbactam[r] (30 mg/kg, IV, q 6 h) for possible gastrointestinal translocation secondary to the severe diarrhea and hematochezia, sucralfate[s] (1 g, PO, q 8 h), trazodone[t] (75 mg, NG, q 8 h), and acepromazine[u] (5 μg/kg, IV, as needed). On day 2, the dog was cardiovascularly stable with normal vital signs. The dog ate a small amount of food and tolerated NG tube feedings at 50% resting energy requirement, which was calculated using the linear equation (body weight in kg × 30 + 70) with a commercially available diet.[v] CBC on day 2 revealed a mild anemia, and biochemistry revealed mild hypoalbuminemia and hypoproteinemia (Table 1), with no evidence of acute kidney injury or hepatotoxicity. The hypoproteinemia and mild anemia were suspected to be sequelae of the manual plasma exchange or secondary to gastrointestinal bleed. The dog's hematochezia slowly improved by day 3 of hospitalization, and the level of care was de-escalated, including discontinuation of ampicillin–sulbactam,[t] cholestyramine,[w] misoprostol,[q] and N-acetylcysteine.[r] On day 3 of hospitalization, the patient was noted to be hypomagnesemic (1.5 mg/dl); therefore, an additional bolus of magnesium sulfate[x] (0.3 mEq/kg, IV) was given. The dog exhibited 2 isolated incidents of regurgitation, and ondansetron[y] (1 mg/kg, IV, q 8 h) was added to the treatment plan. The dog was weaned off IV fluids and metoclopramide[m] on day 4 of hospitalization, and CBC and biochemistry performed on day 5 were within normal limits. The dog was discharged from the hospital on day 5. Recheck bloodwork performed 12 days after initial ingestion was within normal limits with no evidence of organ dysfunction.

Plasma samples were collected from the dog prior to initiation of manual plasma exchange and immediately following completion of 12 cycles of manual plasma exchange. High-pressure liquid chromatography with fluorescence detection was used for quantification of carprofen in canine plasma. Pre-exchange carprofen level was 238.5 ppm and post-exchange carprofen level was 102.5 ppm, indicating a 57% decrease in plasma carprofen.[a]

3 | DISCUSSION

Acute carprofen overdose is a common toxicosis that is associated with severe systemic consequences. Treatment of toxicity is often centered around decontamination techniques and supportive care that often includes induction of emesis and administration of activated charcoal or IV lipid emulsion. Multidose charcoal has been documented to decrease maximum plasma concentration and half-life of carprofen ingestion at doses of 120 mg/kg and, in addition, IV lipid emulsion has been documented to decrease serum naproxen levels.[9,10] In addition to conventional management, advanced and specialized techniques including hemodialysis, hemoperfusion, and TPE have been investigated as adjunctive therapies. TPE has been

a successful adjunctive treatment due to its ability to remove drugs and toxins that are highly protein bound with a small volume of distribution.[11,12]

TPE involves the processing of blood in order to remove the plasma component of blood, which is then replaced with a combination of fluids that includes plasma, albumin, synthetic colloids, and crystalloids. TPE utilizes centrifugal techniques to separate cellular and noncellular components of blood through a semipermeable membrane.[16] Centrifugal TPE separates plasma from the cellular components of blood based on density, which is the principle behind manual plasma exchange.[17] Once the whole blood is separated into plasma and RBC components, the plasma fractions containing protein-bound substances are discarded, and the RBCs are returned to the patient with replacement fluids.[13,18] Membrane-based TPE uses a continuous extracorporeal unit and hollow-fiber plasma separator to retain cellular elements and filter out plasma.[16]

TPE, utilizing either mechanism of plasma removal, results in rapid removal of toxic substances from blood, and automatic sessions can often be completed rapidly, in as little as 2–3 hours.[12,19] TPE was used in a dog ingesting 72 mg/kg of carprofen, and a 51% decrease in plasma carprofen levels was noted.[11] While TPE has been documented as a promising adjunctive technique in the management of NSAID toxicosis, including carprofen, ibuprofen, meloxicam, naproxen, and deracoxib, its use is limited due to lack of equipment and expertise availability.[12,14,20] The machine and expertise required for TPE is uncommon and is limited to select university and specialty hospitals worldwide. Although machine-based TPE is preferred, when not available, manual plasma exchange is a potential alternative solution. In manual plasma exchange, whole blood is removed from the patient in cycles and centrifuged to separate the blood into plasma and cellular components.[21] Once the whole blood is separated into components, the plasma is discarded and the remaining cellular components are returned.[20] Additionally, patient volume is replaced utilizing crystalloids and often a combination of natural and synthetic colloids. Manual TPE is technically simple, and the only equipment required is a large blood centrifuge, which is common in university and specialty practice settings. In addition to its potential use in the treatment of toxicities, such as in this case, manual plasma exchange has been reported to be successful in veterinary clinical scenarios such as hepatic encephalopathy and kernicterus.[22,23] Although technically simple, in comparison to machine-based plasma exchange, manual plasma exchange is extremely time- and labor-consuming, which may result in decreased effectiveness. The time commitment to manual plasma exchange is substantially longer than machine-based TPE. While beneficial as an adjunctive for management of toxicities and other disease processes, the most common complications associated with TPE in veterinary medicine include vomiting, hemorrhagic diarrhea, hypocalcemia, systemic clotting, infection, and technical problems.[16] An additional complication with TPE includes hypovolemia due to volume removal, as was suspected in this case. While manual plasma change can be performed successfully, monitoring of common complications including hypocalcemia and hypovolemia is essential. Manual TPE has been successfully described in veterinary medicine. This is the first case report describing its success in a case of carprofen toxicity.

Carprofen overdose at 223 mg/kg in this case may have resulted in systemic consequences, including severe gastrointestinal ulceration, acute kidney injury, and potentially hepatotoxicity. The dog in this case report developed gastrointestinal upset that included mild regurgitation and hematochezia and evidence of hypovolemia, which was suspected to be secondary to the combination of gastrointestinal losses and manual TPE. These complications associated with the carprofen ingestion and manual TPE resolved readily with supportive care, and the dog never developed any evidence of acute kidney injury or hepatotoxicity. The mild anemia and hypoalbuminemia were attributed to the exchange and resolved within 3–4 days of hospitalization without intervention. Minimal complications were associated with the exchange process, and the period of instability on the first night of hospitalization was attributed to hypovolemia secondary to gastrointestinal losses in combination with the manual exchange.

In this case, the combination of decontamination techniques, supportive care, and manual TPE resulted in a 57% decrease in plasma carprofen levels, similar to a previously reported decrease of 51% utilizing an automated system.[11] While it is impossible to note the percent of decrease in plasma carprofen levels solely attributed to the manual plasma exchange due to the multimodal approach in this case, including the utilization of activated charcoal,[c] cholestyramine,[d] and IV lipid emulsion,[e] previous reports have noted that none of the adjunctive treatments had statistically significant relationships with the outcome in canine TPE for NSAID overdose.[14] It is certain that the decrease of plasma carprofen in the case was attributed to not only the manual plasma exchange but the combination of plasma exchange and previously described decontamination techniques. This case demonstrates a technically simple, manual approach to TPE that may be effective in the treatment of severe carprofen overdose, in combination with adjunctive decontamination therapies including activated charcoal,[c] cholestyramine,[d] and IV lipid emulsion.[e]

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTES

[a] Carprofen (rimadyl), Zoetis LLC, Lincoln, NE.
[b] Apormorphine, Iowa State University, Ames, IA.
[c] Activated charcoal, Lloyd Inc, Shenandoah, IA.
[d] Maropitant, Zoetis LLC, Kalamazoo, MI.

[e] Intralipid, Fresnius Kabi, Deerfield, IL.
[f] Butorphanol, Zoetis LLC, Kalamazoo, MI.
[g] Dexmedetomidine, Zoetis LLC, Kalamazoo, MI.
[h] Anticoagulant citrate dextrose solution (ACD), Baxter Healthcare, Marion, NC.
[i] 0.9% sodium chloride injection, Hospira Inc, Lake Forest, IL.
[j] Vetstarch, Zoetis LLC, Kalamazoo, MI.
[k] 0.45% sodium chloride injection, Baxter, Deerfield, IL.
[l] Metoclopramide, Hospira Inc, Lake Forest, IL.
[m] Hypertonic saline, Nova-Tech Inc, Grand Island, NE.
[n] Pantoprazole, West-ward, Eatontown, NJ.
[o] Misoprostol, Novel Laboratories Inc, Somerset, NJ.
[p] N-acetylcysteine, Hospira Inc, Lake Forest, IL.
[q] Metronidazole, Hospira Inc, Lake Forest, IL.
[r] Unasyn, AuroMedics Pharma LLC, Windsor, NJ.
[s] Sucralfate, TEVA, North Wales, PA.
[t] Trazodone, Major Pharmaceuticals, Livonia, MI.
[u] Acepromazine, MWI, Boise, ID.
[v] Royal Canin GI low fat, Royal Canin USA Inc, St. Charles, MO.
[w] Cholestyramine, Zydus Pharmaceuticals, Pennington, NJ.
[x] Magnesium sulfate, Fresenius Kabi, Lake Zurich, IL.
[y] Ondansetron, Accord Healthcare Inc, Durham NC.

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