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STANDARD ARTICLE

Use of therapeutic plasma exchange to treat nonsteroidal anti-inflammatory drug overdose in dogs

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Background: Therapeutic plasma exchange (TPE) may be an effective technique for treatment of accidental nonsteroidal anti-inflammatory drug (NSAID) overdose, but information regarding the use of this technique in veterinary medicine is currently limited.

Objectives: To evaluate the overall outcome for dogs with NSAID overdose treated with TPE and to determine if any presenting factors can predict or influence overall outcome. Secondary objectives included investigating TPE complications as well as the utility of other adjunctive treatments.

Animals: Eleven client-owned dogs presented for NSAID overdose that received TPE. All patients also received additional supportive treatment including IV lipid infusion.

Methods: Retrospective review of medical records.

Results: Eleven cases were included in the study. Of these, the NSAID ingested was ibuprofen in 6 (54.5%), naproxen in 4 (36.4%), and deracoxib in 1 (9.1%). All dogs survived to discharge with 3 (27.3%) developing acute kidney injury during hospitalization. A larger initial dose of NSAID ingested was associated with a higher maximum serum creatinine concentration during hospitalization (P = .04) and larger change in serum creatinine concentration from baseline (P = .02). Six dogs (54.5%) developed complications associated with TPE. The use of other treatments did not affect the overall outcome.

Conclusions and Clinical Importance: We identified TPE as an effective treatment for NSAID overdose with good outcomes despite high doses of NSAID ingestion in dogs treated with a single TPE treatment. Complications were common but did not affect the final outcome. Therapeutic plasma exchange should be considered in patients presenting for high-dose NSAID ingestion.

KEYWORDS

acute kidney injury, deracoxib, dog, hemodialysis, ibuprofen, naproxen, plasmapheresis, toxicity

1 | INTRODUCTION

Therapeutic plasma exchange (TPE) or plasmapheresis is a technique wherein a patient's blood is processed to separate the cellular components from the plasma.[1] This separation occurs in an extracorporeal blood purification circuit and can be performed through hollow fiber plasma filters or with a centrifugal cell separator.[2] The primary purpose of this technique is to remove harmful components from the patient's plasma. Plasmapheresis has been performed in veterinary medicine since in the 1980s and remains relevant today for a variety of conditions such as immunologic diseases,[3–7] *Ehrlichia canis* infection,[8] kernicterus,[9] and multiple myeloma.[10] Recently, 3 case reports have described the use of TPE for ibuprofen,[11] meloxicam,[12] and carprofen[13] overdose.

The value of TPE for treating toxicities has been well established in the human medical literature.[14,15] The utility of TPE varies depending on the characteristics of the particular toxin, and this technique is

Abbreviations: ACT, activated clotting time; AKI, acute kidney injury; CKD, chronic kidney disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; TPE, therapeutic plasma exchange; V_d, volume of distribution.

particularly suited to toxins with high levels of protein binding and a low volume of distribution (V_d).[15]

Therapeutic plasma exchange carries some risks, and several complications have been reported in the human medical literature.[16,17] The most common complications include patient discomfort and minor technical complications, although more serious issues such as hypotension, allergic reactions, bleeding, clot formation, and sepsis also have been reported.[16] Although similar complications likely also occur in veterinary patients, the largest published study so far consisted of 5 patients,[3] and thus an evaluation of complication frequency has not been performed.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in both humans and animals as analgesics. These medications inhibit cyclooxygenase, which is involved in the production of prostanoids (including prostacyclin, prostaglandins, and thromboxanes). Numerous adverse effects of NSAID use and intoxication have been reported in veterinary medicine including vomiting, diarrhea, anorexia, melena, kidney injury, and central nervous system effects (seizures, ataxia, or coma).[18–20] Traditionally, treatment of NSAID toxicity has been limited to supportive and symptomatic treatment including aggressive decontamination, IV fluid administration, gastrointestinal (GI) protectant medications, antiemetics, and prostaglandin analogs, with the recent addition of IV lipid emulsion as a treatment option.[21,22] However, extracorporeal blood purification treatments have been emerging as additional options for management of NSAID toxicity in animals. Recently, 3 case reports about the use of TPE for the treatment of overdoses of meloxicam,[12] ibuprofen,[11] and carprofen[13] have been published. Also, the use of charcoal hemoperfusion and hemodialysis for ibuprofen toxicity in a dog[23] has been reported. Nonsteroidal anti-inflammatory medications are highly protein bound (98%-99%) and have a small V_d,[18] which makes them difficult to remove by hemodialysis alone, but are ideal candidates for TPE or charcoal hemoperfusion techniques.

Our primary objective was to evaluate patients treated for NSAID overdose using TPE at our institution and to determine if any variables at presentation predicted the outcome and risk of developing kidney injury. Secondary goals were to identify any risk factors associated with TPE complications in these patients and to determine the effect of other adjunctive treatments.

2 | MATERIALS AND METHODS

2.1 | Case selection

A retrospective review of medical records from the Foster Hospital for Small Animals at the Cummings Veterinary Medical Center at Tufts University was performed for all dogs that underwent TPE between January 1, 2015, and May 31, 2017. Cases were included if the patients were presented for ingestion of an NSAID at above the recommended dosage and if the primary indication for TPE was treatment of NSAID intoxication.

2.2 | Medical records review

Details extracted from the medical record included signalment (age, sex, body weight, and breed), clinical and laboratory findings on presentation, details regarding treatment and clinicopathologic findings during hospitalization, and outcome. Details about presentation included the presence of any clinical signs before presentation, which NSAID was ingested, the estimated amount of NSAID ingested, the time since ingestion, and the initial laboratory findings (including serum biochemistry, urinalysis, and PCV). Records were reviewed for which adjunctive and supportive treatments the patients received during hospitalization, including the use of activated charcoal (ToxiBan; Lloyd, Inc, Shenandoah, Iowa), induction of emesis, IV lipid infusion (Intralipid; Baxter Healthcare Corp, Deerfield, Illinois), IV fluids, and the use of any GI protective agents.

All patients underwent a single TPE treatment using a membrane filtration–based plasmapheresis unit (Prismaflex; Gambro Lundia AB, Lund, Sweden). Target plasma exchange volumes were calculated for each patient using a goal of either 1.0 or 1.5 patient plasma volumes exchanged. Each patient's plasma volume was calculated using the following equation: plasma volume = 0.08 × body weight × (1 − PCV). This equation is derived from the calculation of the patient's whole blood volume (80 mL/kg) multiplied by the percentage of that blood volume that consists of plasma.[24] The decision on each patient's goal was based on the total amount of NSAID ingested, with most patients having a goal of 1.5 plasma volumes exchanged because of the large amount of NSAID ingested. This value is taken from calculations involving the pharmacokinetics of solute removal that describe the amount of a substance expected to be removed based on the number of total plasma exchanges performed, which is 63% at 1 plasma exchange and 78% at 1.5 plasma exchanges.[25] The rate and duration of the treatment session were determined based on a target filtration fraction of 20%. The patients received approximately 50% of the replacement fluid as fresh-frozen type-matched canine plasma, with the remainder being given as a colloid solution (6% hydroxyethyl starch [Vetstarch; Zoetis, Kalamazoo, Michigan]). The target amount of plasma was 50%, but patients received a range of plasma volumes in their replacement solutions. This data was collected and included in the analysis.

All patients were anesthetized for placement of a dual-lumen hemodialysis catheter in an external jugular vein (Makurkar; Covidien, Mansfield, Massachusetts). Catheter size was chosen based on patient size and conformation, with the smallest size used being an 8-French, 12-cm-long catheter and the largest being a 13.5-French, 19.5-cm long catheter. The catheters were placed using a modified Seldinger technique. All patients received heparin infusions during treatment for anticoagulation, starting with a heparin bolus of 25 units/kg and an initial continuous infusion rate of 20-25 units/kg/h. Activated clotting time (ACT) was monitored every 15 minutes near the beginning of treatment, and changes to the heparin infusion rate (and additional intermittent heparin boluses if needed) were made to meet a target ACT range. The target ACT was determined for each individual patient based on blood flow rate and time for the blood to be in the extracorporeal circuit but in general was between 180 and 300 seconds. Once the target ACT was met, additional ACT measurements were performed every 30 minutes for the duration of treatment, with rechecks being performed every 15 minutes if the measured ACTs were outside the target range. Additional details of the TPE treatment were extracted from the TPE records including time elapsed between toxin

ingestion and start of the session, duration of the session, total volume of plasma replaced, number of patient plasma volumes exchanged, ACT results during the treatment, amount of heparin (Heparin Sodium; Sagent Pharmaceuticals, Schaumburg, Illinois) given, and whether or not any adverse events occurred during or after treatment.

Data regarding the outcome were extracted from the medical record including days spent in the hospital, development of GI signs or acute kidney injury (AKI), maximum serum creatinine concentration during hospitalization and change in serum creatinine concentration from baseline, and overall outcome (survival as well as development of chronic kidney disease [CKD] after discharge). Development of AKI was defined as an increase in serum creatinine concentration of at least 0.3 mg/dL.[26] Factors investigated with regard to outcome included which NSAID was ingested, amount of NSAID ingested, presence of clinical signs (neurologic or GI) at presentation, time between ingestion and presentation as well as time between ingestion and start of TPE, laboratory results at presentation (serum creatinine, blood urea nitrogen, albumin, phosphorus, and potassium concentrations and PCV), and variables associated with the TPE session (duration of session, total volume exchanged, patient plasma volumes exchanged, and development of complications). Urinalysis data was only available for 4 dogs (36.4%), and only 1 of which had an increased serum creatinine concentration. Because so few patients had urinalyses performed, urinalysis results were excluded from further evaluation.

Records were reviewed for any evidence of complications associated with TPE that occurred during or after treatment, and the type of complication was recorded. Variables investigated regarding likelihood of complications included patient body weight, clinicopathologic data at presentation (serum albumin, potassium and sodium concentrations, PCV, and platelet count), TPE session parameters (duration of session, plasma volumes exchanged, plasma volume given as replacement, colloid volume given as replacement, and total amount of heparin infused), and minimum and maximum ACT results measured during treatment.

2.3 | Statistical methods

Descriptive statistics were calculated. The Shapiro-Wilk test was done to evaluate data for normality. Bivariate statistics were performed to determine associations between various factors and categorical outcomes, including development of AKI, presence of GI signs, and occurrence of complications, with Fisher's exact test being used when the factor was categorical and a *T*-test being used when the data were continuous. Linear regression models were used to evaluate the effect of various factors on continuous outcomes (maximum serum creatinine concentration during hospitalization, change in serum creatinine concentration, and days of hospitalization). Statistical analysis was performed using commercial software (SAS Version 9.4; SAS Institute Inc, Cary, North Carolina). In analyses, values of $P < .05$ were considered significant.

3 | RESULTS

Eleven dogs received TPE for NSAID overdose during the examined time period. The median age was 3 years (range, 2 months to 11 years). Sex distribution was 7 (63.6%) neutered males, 2 (18.2%) spayed females, 1 (9.1%) intact male, and 1 (9.1%) intact female. Mixed breed dogs,[3] Golden Retrievers,[2] and Labrador Retrievers[2] were the most common breeds, followed by 1 dog each from the Basset Hound, Dachshund, German Shepherd, and Papillon breeds. Median body weight was 12 kg (range, 4.2-28.4 kg).

The NSAID ingested was ibuprofen (multiple brands available including Motrin; Johnson & Johnson Consumer Inc, Fort Washington, Pennsylvania) in 6 dogs (54.5%), naproxen (multiple brands available including Aleve; Bayer Healthcare LLC, Morristown, New Jersey) in 4 dogs (36.4%), and deracoxib (Deramaxx; Elanco US Inc, Greenfield, Indiana) in 1 dog (9.1%). The median amount of NSAID ingested per kilogram of body weight was 306 mg/kg (range, 26-1480 mg/kg), with the median amount of ibuprofen ingested being 774.5 mg/kg (range, 283-1480 mg/kg), naproxen being 129.5 mg/kg (range, 26- 695 mg/kg), and deracoxib 95 mg/kg (1 case).

The time that had passed between ingestion of the NSAID and presentation or initiation of TPE was known for 9 dogs (81.8%) to be within 1 hour, and a maximum potential time had to be used as an estimate for the remaining 2 dogs. The median time between NSAID ingestion and presentation was 4.5 hours (range, 1-12 hours), and the time between ingestion and initiation of TPE was 8 hours (range, 4.5-17 hours). Each patient had a single TPE session performed over a median of 2.0 hours (range, 1.25-3.5 hours).

3.1 | Overall outcome and probability of developing toxicity

Of the 11 cases, 3 (27.3%) dogs developed AKI, as defined by an increase in serum creatinine concentration of at least 0.3 mg/dL from baseline, and 6 (52.5%) developed GI signs. When development of AKI and GI signs were considered as categorical variables, none of the examined factors was predictive (see Table 1).

The maximum serum creatinine concentration during the course of hospitalization of these patients was 1.57 ± 1.07 mg/dL, with an average change in serum creatinine concentration from presentation to a maximum of 0.55 ± 1.02 mg/dL. Amount of NSAID ingested (per kilogram body weight) was associated with a higher maximum serum creatinine concentration ($P = .04$) and a larger change in serum creatinine concentration from baseline ($P = .02$). No other variable regarding elapsed time, examination or laboratory findings at presentation, or TPE parameters had a significant effect on the maximum serum creatinine concentration during hospitalization or change in serum creatinine concentration during hospitalization (see Table 2).

Dogs were hospitalized for a mean of 2.8 ± 1.8 days. The only variable with a significant effect on duration of hospitalization was PCV at presentation ($P = .005$).

All patients survived to discharge. Only 6 dogs (54.5%) had follow-up information after discharge from the hospital. Of these dogs, only 1 had persistently increased serum creatinine concentration and thus was thought to have developed CKD. This dog had ingested the largest amount of NSAID at 1480 mg/kg of ibuprofen. In addition, this dog had developed AKI in the hospital and had the highest serum creatinine concentration (4.3 mg/dL) and change in serum creatinine concentration (3.2 mg/dL) of all dogs while hospitalized.

TABLE 1 Value of presenting findings and TPE parameters for predicting the development of toxicity (AKI or GI signs)

	AKI			GI		
Factors	Yes (n = 3) N (%)	No (n = 8)	*P*-value	Yes (n = 6) N (%)	No (n = 5)	*P*-value
NSAID			.99			.55
Ibuprofen	2 (66.7)	4 (50.0)		3 (50.0)	3 (60.0)	
Naproxen	1 (33.3)	3 (37.5)		3 (50.0)	1 (20.0)	
Deracoxib	0 (0.0)	1 (12.5)		0 (0.0)	1 (20.0)	
Presenting GI signs			.55			>.99
Yes	2 (66.7)	3 (37.5)		3 (50.0)	2 (40.0)	
No	1 (33.3)	5 (62.5)		3 (50.0)	3 (60.0)	
Presenting neurologic signs			.49			.55
Yes	0 (0.0)	3 (37.5)		1 (16.7)	2 (40.0)	
No	3 (100.0)	5 (62.5)		5 (83.3)	3 (60.0)	
TPE complications			.99			.99
Yes	2 (66.7)	4 (50.0)		3 (50.0)	3 (60.0)	
No	1 (33.3)	4 (50.0)		3 (50.0)	2 (40.0)	
	Mean ± SD		*P*-value	Mean ± SD		*P*-value
Dose (mg/kg)	951.3 ± 457.9	361.9 ± 386.6	.06	544.2 ± 540.1	496.8 ± 435.7	.88
Time (presentation) (h)	4.2 ± 5.1	5.1 ± 2.5	.69	5.7 ± 3.7	3.8 ± 2.2	.35
Time (TPE) (h)	7.2 ± 4.2	8.6 ± 2.4	.50	9.0 ± 3.4	7.2 ± 1.9	.32
Albumin (g/dL)	3.4 ± 0.6	3.5 ± 0.4	.59	3.6 ± 0.5	3.4 ± 0.5	.63
BUN (mg/dL)	17.0 ± 8.7	18.6 ± 3.5	.78	19.2 ± 6.2	17.0 ± 3.0	.50
Creatinine (mg/dL)	1.0 ± 0.1	1.0 ± 0.3	.73	1.1 ± 0.2	0.9 ± 0.2	.08
Phosphorus (mg/dL)	5.1 ± 1.5	5.1 ± 2.1	.96	4.8 ± 1.3	5.6 ± 2.6	.55
Potassium (mmol/L)	4.6 ± 0.3	4.7 ± 0.5	.96	4.6 ± 0.3	4.7 ± 0.7	.66
PCV (%)	45.3 ± 4.5	49.3 ± 8.2	.46	46.7 ± 3.7	50.0 ± 10.6	.53
TPE duration (h)	2.1 ± 1.2	2.2 ± 0.5	.87	2.3 ± 0.9	2.1 ± 0.4	.73
Total replacement (mL)	1000.0 ± 700.0	765.6 ± 410.5	.50	756.7 ± 581.8	917.0 ± 359.4	.61
Plasma volumes exchanged	1.1 ± 0.7	1.1 ± 0.5	.98	1.0 ± 0.5	1.2 ± 0.5	.45

Time (presentation) indicates time between ingestion of NSAID and presentation at the hospital, and time (TPE) indicates time between ingestion of NSAID and initiation of TPE. Continuous variables reported as mean ± SD.
Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; TPE, therapeutic plasma exchange.

TABLE 2 Correlation by linear regression of patient history at presentation, presenting laboratory findings, and TPE parameters on the maximum creatinine reached during hospitalization

	Mean ± SD	*P*-value
Time (presentation) (h)	4.8 ± 3.1	.35
Time (TPE) (h)	8.2 ± 2.8	.18
NSAID dose (mg/kg)	522.6 ± 471.6	.04
Albumin (g/dL)	3.5 ± 0.44	.99
BUN (mg/dL)	18.2 ± 4.9	.23
Creatinine (mg/dL)	1.0 ± 0.23	.27
Phosphorus (mg/dL)	5.1 ± 1.8	.70
Potassium (mmol/L)	4.6 ± 0.47	.84
PCV (%)	48.2 ± 7.4	.76
Duration of session (h)	2.2 ± 0.67	.15
Total replacement (mL)	829.5 ± 477.4	.16
Plasma volumes exchanged	1.08 ± 0.5	.91

Time (presentation) indicates time between ingestion of NSAID and presentation at the hospital, and time (TPE) indicates time between ingestion of NSAID and initiation of TPE. Continuous variables reported as mean ± SD.
Abbreviations: BUN, blood urea nitrogen; NSAID, nonsteroidal anti-inflammatory drug; TPE, therapeutic plasma exchange.

3.2 | Complications associated with TPE

Six dogs (54.5%) developed complications associated with TPE. Complications associated with hemostasis were found most commonly with evidence of bleeding found in 3 dogs (27.3%) and clotting identified during the TPE session in 2 dogs (18.2%). Bleeding was identified as hematoma formation around the jugular catheter in 2 dogs and hematuria in 1 dog, all of which were identified between 12 and 24 hours after the TPE session. Although a small amount of bleeding or bruising near the catheter insertion site can be seen as a consequence of catheter placement, these 2 patients had substantial SC hematoma formation that required having a pressure wrap applied for an additional day in hospital. In addition, 2 of these patients (1 with a hematoma and 1 with hematuria) had prolonged ACT when measured at the time of the bleeding event, supporting that the bleeding was related to an abnormality of coagulation. Clotting was only identified as large blood clots in the TPE filter, and no dogs had clinical signs associated with clotting. Both these patients had increases in transmembrane pressure during the TPE session as well as having large clots visible within the filter, which necessitated pausing the session

TABLE 3 Value of presenting laboratory findings and TPE parameters on likelihood of the development of hemorrhagic complications during or after TPE

	Yes (n = 3)	No (n = 8)	*P*-value
Body weight (kg)	14.5 ± 11.0	18.9 ± 9.9	.55
Albumin (g/dL)	3.6 ± 0.1	3.5 ± 0.5	.72
Potassium (mmol/L)	4.4 ± 0.1	4.7 ± 0.5	.39
Sodium (mmol/L)	153.0 ± 6.1	146.9 ± 2.8	.04
PCV (%)	50.7 ± 6.7	47.3 ± 7.9	.53
Platelets (thou/μL)	270 ± 108.9	218.9 ± 43.4	.30
Duration of Session (h)	2.5 ± 1.0	2.1 ± 0.5	.36
Minimum ACT (s)	999 ± 0.0	395.6 ± 366.6	.08
Maximum ACT (s)	999 ± 0.0	759.6 ± 409.3	.36
Total heparin (U/kg)	155.4 ± 181.3	82.2 ± 61.6	.31
Plasma volumes exchanged	1.5 ± 0.5	0.9 ± 0.5	.12
Plasma replacement (mL)	245 ± 8.7	366.9 ± 273.4	.47
Plasma replacement (%)	46.4 ± 8.2	46.7 ± 27.8	.98
Colloid replacement (mL)	761.7 ± 453.2	700 ± 420.9	.84

Values are reported as mean ± SD. Plasma replacement (%) indicates the percentage of the total replacement fluid that was given as plasma.
Abbreviations: ACT, activated clotting time; TPE, therapeutic plasma exchange.

so that the filter and lines could be replaced. One dog (9.1%) developed hypotension during the TPE session.

None of the investigated variables had a significant predictive effect on the likelihood of TPE complications in general or on the development of filter clotting. A higher serum sodium concentration was significantly (P = .04) associated with a higher risk of bleeding (see Table 3).

3.3 | Efficacy of other treatments during hospitalization

In addition to TPE, all dogs received other treatments during hospitalization. All 11 dogs received IV fluid therapy, IV lipid infusions, and pantoprazole (Protonix; Wyeth Pharmaceuticals Inc, Philadelphia, Pennsylvania). Lipid treatment was given according to standard protocol at our institution, which was an initial bolus of 1.5 mL/kg given over 1 minute, followed by a constant rate infusion of 0.25 mL/kg/min over 30-60 minutes. All patients received lipid treatment before receiving TPE, and no patient had additional doses of IV lipids after this initial infusion. Nine of 11 dogs (81.8%) had emesis induced on presentation, 9 (81.8%) were given activated charcoal, 7 (63.6%) received misoprostol (Novel Laboratories, Inc., Somerset, New Jersey), 8 (72.7%) received sucralfate (TEVA Pharmaceuticals USA, Inc, North Wales, Pennsylvania), and 4 (36.4%) received metronidazole (Hospira, Inc, Lake Forest, Illinois). Dogs received a median of 2 doses (range, 1-5 doses) of activated charcoal. None of these adjunctive treatments had a statistically significant relationship with any of the outcomes examined (ie, development of AKI or GI signs, maximum or change in serum creatinine concentration, or days of hospitalization).

4 | DISCUSSION

Therapeutic plasma exchange was successfully performed in 11 dogs presented for acute NSAID overdose. All patients survived to discharge, and only 1 patient, that had ingested the highest amount of NSAID and developed the most severe AKI during hospitalization, went on to develop CKD. The only factor that could accurately predict an increase in serum creatinine concentration after TPE was the initial amount of NSAID ingested (per kilogram body weight). The most commonly ingested NSAIDs were ibuprofen and naproxen, both of which are over-the-counter medications designed for use in humans. Signs of toxicity were identified in most of these dogs with 52.5% developing GI signs and 27.3% developing AKI. Dogs presented with lower initial PCV had a longer hospitalization.

Complications from TPE were commonly observed with 54.5% of cases experiencing a complication, including evidence of clotting, hemorrhage, or hypotension. However, the occurrence of a complication did not have a significant effect on final outcome. A higher serum sodium concentration at presentation increased the risk of hemorrhage during or after TPE. Finally, none of the other treatments that these patients received had a significant impact on outcome.

Of note, all the patients in the study also were treated with IV lipid treatment, which is a standard acute intervention at our institution for patients presenting for NSAID toxicity. The use of IV lipid emulsion treatment has shown great promise in a case report of ibuprofen overdose[21] and in 3 cases of naproxen overdose.[22] Unfortunately, the effect that lipid treatment had on outcomes in our patients could not be fully evaluated because all patients received this treatment, and there was no control group that did not receive lipids. Lipid treatment also has the potential to alter the pharmacokinetics of NSAIDs, with the goal of causing more rapid elimination, which may affect the efficacy of TPE after its use. Regardless, it is impossible to infer from our study the different benefits of IV lipid treatment and TPE on patients with NSAID toxicity. Ideally, additional studies on the use of IV lipid treatment will clarify the results of these initial case reports[21,22] and further elucidate the role this treatment has in patients with NSAID overdose.

Nonsteroidal anti-inflammatory drugs have long been recognized as a potential toxicity risk in both human and veterinary medicine.[18,27,28] Complications associated with NSAID ingestion include GI irritation or ulceration, AKI, central nervous system effects, ataxia, cardiac effects, and hepatotoxicity.[18,21,27] Toxicity has been reported both with overdoses as well as with standard therapeutic doses of NSAIDs.[18–20] In addition, although NSAIDs labeled for use in veterinary patients typically are obtained by prescription, multiple over-the-counter NSAIDs designed for use in humans are available. Our results suggest that the more common source of large NSAID overdoses in veterinary patients is over-the counter medications, because most of these patients presented for ingestion of ibuprofen or naproxen, with only 1 dog presenting for ingestion of an overdose of a veterinary prescription medication (deracoxib).

A previous study on ibuprofen overdose indicated that GI and renal consequences were common, with 55.5% and 55.6% of dogs developing these complications, respectively.[20] In our study, a similar number (54.5%) demonstrated GI signs, with fewer (27.3%) having evidence of AKI. This difference is likely because of the additional treatments our patients received, including TPE and IV lipid treatment. The frequency of GI signs in both studies is very similar, which may be related to the rapidity of development of GI complications compared to the delay in developing clinically recognizable kidney injury.[18] This hypothesis is

supported by the observation that 5 dogs (45.5%) in our study presented having already developed signs of GI toxicity (primarily vomiting and regurgitation). In addition, the amounts of NSAID ingested were higher than those in a previous report in which only 27.6% of cases of ibuprofen ingestion were at a dosage higher than 200 mg/kg.[20] As a comparison, the lowest amount of ibuprofen ingested by dogs in our study was 283 mg/kg, with a range of 283-1480 mg/kg.

Although TPE is not a new technique in veterinary medicine, with multiple reports of its use in the 1980s,[3,4,7,8,29] there are few reports of its use for toxicity cases. In the past 2 years, 3 case reports of the use of TPE for NSAID overdose have been published for ingestions of meloxicam,[12] ibuprofen,[11] and carprofen.[13] Although all these were single case reports, the results were promising, with good clinical outcomes and evidence of an 82% reduction in plasma meloxicam concentrations,[12] an 85% reduction in plasma ibuprofen concentrations,[11] and a 51% decrease in plasma carprofen concentrations.[13] A limitation of our study is that plasma concentrations of the NSAIDs were not measured, and it is impossible to say how much of a decrease was achieved. The average number of plasma exchanges performed in our study was 1.08 ± 0.5, which should translate into an expected 67% decrease in plasma concentration of NSAID, although this is only an estimation.

The primary factor we identified that influenced outcome was the overall amount of NSAID ingested (per kilogram body weight). The role of dosage in NSAID toxicity previously has been investigated with different doses predicting the likelihood of developing GI signs or renal impairment.[18] In addition, the pharmacokinetics of certain NSAIDs is affected by the dose ingested, so that ingestion of a higher dose, as occurs in accidental overdose, can prolong the half-life of these medications and promote further toxic effects.[18] Of note, the dogs in our study likely do not represent the entire population of dogs presenting for NSAID ingestion. Therapeutic plasma exchange was only recommended for dogs with large amounts of NSAID ingestion that exceeded the amounts recognized to cause substantial renal impairment, and only such cases were considered in our study. It is probable that TPE is less necessary in animals presented for smaller amounts of NSAID ingestion, in which decontamination and supportive care may be sufficient.

We also identified that patients presented with lower PCV had significantly longer durations of hospitalization, although this did not change the overall outcome or likelihood of developing kidney disease. The most likely explanation is that time of discharge from the hospital was determined largely by the progression of AKI, management of GI signs, or the resolution of any TPE complications. A low PCV could be interpreted as a sign of GI ulceration or as evidence of hemorrhage as a TPE complication, and thus it is likely that these patients were hospitalized for a longer course of treatment and monitoring before discharge.

An additional important finding of our study was the frequency of complications associated with TPE, with over half of patients developing some complication. In human medicine, the complication rate for TPE ranges from 25.6% to 36%.[16,17] The most commonly observed complications in humans include fever, urticaria, or mild technical complications associated with blood flow.[16,17] In reports of humans, complications associated with thrombosis or hemorrhage are rare and occur in fewer than 1.5% of cases.[16,17] The cause of the increased frequency of complications in veterinary medicine compared to human medicine is likely multifactorial. One difficulty is that the average veterinary patient is much smaller, thus leading to slower blood flow through the circuit and a larger portion of the patient's blood being in the extracorporeal circuit at any time. An additional factor in this particular patient population is that NSAIDs have been shown to have various effects on coagulation parameters in dogs,[30] and thus patients presented for NSAID overdoses may pose particular difficulties in controlling clotting parameters during TPE. These patients all had their clotting parameters monitored, with adjustment of heparin doses as needed during their TPE sessions, and the data did not indicate any relationship between minimum or maximum ACTs measured during treatment and the risk of bleeding or developing clots in the filter. However, NSAIDs have been shown to have effects on platelet function,[30] and a more complete diagnostic evaluation, including platelet function testing to identify thrombopathias, may be required to fully elucidate these effects.

The only factor that influenced the likelihood of a complication was that patients with higher serum sodium concentrations on presentation had an increased risk of bleeding. The cause of this increased risk is not clear, and it may reflect type I error because only 3 patients (27.3%) had evidence of bleeding, and there is no clear physiologic explanation for a relationship between increased serum sodium concentration and bleeding tendency. Further study with a larger patient population is warranted to further elucidate any factors that may be associated with TPE complications.

The last objective of our study was to identify if treatments other than TPE influenced the overall outcome. Because our study was retrospective, it was not possible to control the other treatments that these patients received. However, most patients received similar treatments consistent with the standards of care at our institution. All patients received IV fluids, IV lipid infusion, and pantoprazole. Most patients had similar decontamination protocols including induction of emesis (81.8%) and 1-5 doses of activated charcoal (81.8%). Most patients also received sucralfate (72.7%), with fewer receiving misoprostol (63.6%) and metronidazole (36.4%). These differences partially were based on clinician preference and partially a response to the clinical signs of individual patients. None of these treatments was shown to significantly change outcome in our patient population, but patient numbers were low because most patients received similar ancillary treatments. The effect of these treatments in conjunction with TPE would be better evaluated using a prospective study design with randomization to determine which treatments to provide. Because most patients in our study received these treatments, it is possible that their elimination would have adversely affected outcome.

The limitations of our study include relatively small case number as well as its retrospective design. Therapeutic plasma exchange is an advanced procedure requiring specialized equipment and training, and thus it is difficult to collect a large patient population to study its use. These factors limit the overall analysis and conclusions that can be drawn from our study, and further studies using a larger population would be valuable as this technique becomes more common. In addition, the retrospective nature of our study meant that the treatments (both adjunctive treatments as well as the TPE protocols) could not be standardized. Similarly, diagnostic testing and monitoring were not standardized, leading to difficulties such as relatively few urinalysis results available from presentation as well as a lack of follow-up data in 45.5% of cases.

In conclusion, our study supports the use of TPE as an adjunctive treatment for dogs ingesting large amounts of NSAIDs. All 11 dogs successfully underwent TPE with 27.3% developing AKI and only 1 dog having evidence of longer term renal impairment. Complication rate was high (54.5%) but did not have an effect on overall outcome or long-term prognosis. Therapeutic plasma exchange should be considered in animals presented for ingestion of nephrotoxic or lethal amounts of NSAIDs.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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