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Outcomes of nonsteroidal anti-inflammatory drug toxicosis treated with therapeutic plasma exchange in 62 dogs

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Abstract

Background: Therapeutic plasma exchange (TPE) is gaining popularity for the management of nonsteroidal anti-inflammatory drug (NSAID) overdose in dogs.

Hypothesis/Objectives: Describe a population of dogs treated with TPE for NSAID overdose.

Animals: Sixty-two dogs with NSAID overdose treated with TPE.

Methods: Multicenter retrospective study of dogs treated with TPE for ibuprofen, carprofen, or naproxen overdose.

Results: The median dose of ibuprofen, carprofen or naproxen ingested was 533 mg/kg (range, 36-4857 mg/kg), 217 mg/kg (range, 88-625 mg/kg) and 138 mg/kg (range, 26-3000 mg/kg), respectively. Based on previously established toxic ranges for each NSAID, 2 (3.2%), 14 (22.6%), and 46 (74.2%) dogs ingested a gastrointestinal, renal, and neurological toxic dose, respectively. The median time between ingestion and presentation was 4 hours (range, 1-20 hours). The median number of plasma volumes processed was 1.6 (range, 0.4-2.2). The median TPE session duration was 2 hours (range, 1-4.5 hours). Circuit clotting developed during 8 (12.9%) sessions. Patient adverse events reported during 21 (33.8%) sessions consisted of urticaria (12.9%), asymptomatic hypocalcemia (9.6%), and hypotension (9.6%). The median duration of hospitalization was 2.25 days (range, 1-11 days). Sixty-one (98.4%) dogs survived to discharge, and none were rehospitalized. Thirty-one (91.1%) of the 34 dogs with at least 1 follow-up visit were not azotemic at the time of reevaluation.

Conclusions and Clinical Importance: This population of dogs managed with TPE had excellent outcomes, even in cases of high NSAID dose ingestion. When TPE is available and the time frame is appropriate, this extracorporeal modality should be considered for the management of NSAID overdose.

KEYWORDS
carprofen, ibuprofen, naproxen, NSAID, TPE

1 | INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most reported poisonings associated with prescription and over-the-counter medications in dogs.[1-4] The therapeutic effects of NSAIDs result from attenuation of eicosanoid production, particularly by inhibition of cyclooxygenase, limiting the synthesis of prostanoids.[5-7] Clinical signs of NSAID intoxication range from mild gastrointestinal (GI) signs to severe acute kidney injury (AKI), with central nervous system (CNS) disturbances arising at maximal doses of exposure.[4,8] Hepatoxicities also have been reported.[4,8,9]

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique that has gained popularity as a management option for NSAID intoxications.[10-14] The pharmacokinetic characteristics of NSAIDs are well suited to clearance by TPE because they have small molecular weights (206.28-273.71 g/mol), are extensively protein bound (96%-99%), and have a low volume of distribution (0.12-0.16 L/kg).[5-7,15-17] In dogs, the elimination half-lives of PO ibuprofen and carprofen are 4.6 and 8 hours, respectively, whereas naproxen has a clinically relevant longer elimination half-life of 74 hours.[5-7,15-17] Despite the small molecular weight of NSAIDs that would make them easily dialyzable, their very high protein binding precludes the use of this treatment modality. The basic principle of TPE relies on the removal of plasma that contains the protein-bound toxicant of interest from the patient and subsequent administration of replacement solutions including donor plasma, colloidal solutions, and crystalloid solutions. Separation of plasma from whole blood can be achieved by either centrifuge-based (cTPE) or membrane-based (mTPE) TPE. In cTPE, a rotating blood chamber uses centrifugal force to separate cellular and acellular blood components by their respective densities. In mTPE, a nonselective membrane filters solutes based on size, allowing proteins to convectively cross a capillary membrane, leaving behind the blood cellular components.[18]

Despite the increased use of TPE for NSAID overdose, publications on the subject have been limited to several case reports[10,12,13] and 2 retrospective studies.[11,14] The purpose of our retrospective multicenter study was to describe a large population of dog treated with either mTPE or cTPE for the management of NSAID overdose. The specific aims were to determine the complications and outcomes associated with this extracorporeal blood purification modality.

2 | MATERIALS AND METHODS

2.1 | Case selection

Medical records of 4 veterinary teaching hospitals (College of Veterinary Medicine, University of Pennsylvania; the Cummings School of Veterinary Medicine, Tufts University; College of Veterinary Medicine, University of Florida; and College of Veterinary Medicine, North Carolina State University) and 1 private emergency and referral hospital (Blue Pearl Pet Hospital, North Carolina) were retrospectively searched to identify all dogs with NSAID ingestion that were treated with TPE between June 1, 2015, and June 30, 2020. Dogs with incomplete medical records were excluded. Preliminary data collection determined that most NSAID ingestions involved ibuprofen, carprofen, or naproxen. As a result, inclusion criteria were limited to these 3 drugs of interest.

2.2 | Medical records review

Data recorded from the medical records included patient signalment, body weight, NSAID type, maximal NSAID dose reported, maximal time to presentation, clinical signs at presentation, baseline and discharge (or last) serum creatinine concentration, and total solids concentrations. Induction and success of emesis, and the following treatments were recorded: activated charcoal, histamine H2-receptor antagonist, proton pump inhibitor and prostaglandin E1 analog. Details regarding TPE prescriptions and sessions (type of TPE; anticoagulation; total replacement volume, plasma volumes exchanged; plasma, colloid and crystalloid replacement; TPE duration; adverse events) and hospitalization time were recorded. The plasma volume for each patient was calculated in milliliters from the total blood volume (80-90 mL/kg) multiplied by (1 − hematocrit). The type of TPE used varied with the institution, dependent upon equipment availability. Clinically relevant hypocalcemia was defined as an ionized calcium concentration ≤0.8 mmol/L.[19] Maximal serum creatinine concentration was defined as the highest serum creatinine concentration associated with the NSAID toxicity as recorded by either the referring veterinarian or the referral hospital at any time throughout hospitalization.

Dogs were classified according to the maximal ingestion dose recorded in the medical record in milligrams of drug per kilogram of body weight (mg/kg). For ibuprofen, GI, renal, and neurologic (CNS) toxic doses were defined as >25, >100, and >400 mg/kg, respectively.[20-22]

For carprofen, GI, renal, and CNS toxic doses were defined as >20, >40, and >200 mg/kg, respectively.[8] For naproxen, GI, renal, and CNS toxic doses were defined as >5, >25, and >50 mg/kg, respectively.[23-26]

Gastrointestinal (GI) signs were defined as clinical signs of vomiting, regurgitation, diarrhea, or dysorexia (anorexia or hyporexia). Gastrointestinal signs on presentation were defined as clinical signs of vomiting, regurgitation, diarrhea, or dysorexia (anorexia or hyporexia) before iatrogenic emesis induction. Acute kidney injury (AKI) was defined as a serum creatinine concentration >1.6 mg/dL, or an increase in serum creatinine concentration >0.3 mg/dL during a 48-hour time interval, and graded according to the International Renal Interest Society (IRIS) AKI grading system for dogs.[27] Baseline serum creatinine concentrations were obtained either from the referring veterinarian or on admission, as available. Neurological signs were defined as the presence of seizure activity, ataxia, or objective evidence of intracranial disease such as abnormal cranial nerve function or an altered state of consciousness.

Survival to discharge was recorded and 1-year survival was defined as cases where confirmatory record of patient euthanasia, death, or survival was present among the medical records 1-year after the date of discharge. Any report of azotemia in the medical record at future follow-up visits was recorded.

2.3 | Statistical methods

Statistical analyses were conducted using a commercial software program (STATA IC, version 16.1, StataCorp LLC, College Station, Texas). The Shapiro-Wilk test was used to assess continuous variables for normality. Descriptive statistics consisted of the median and range for all continuous variables given that most of the variables were not normally distributed. Count and percentage (%) were used to report frequency data. Dichotomous outcome variables were compared using the chi-squared test when cell counts in the 2 × 2 contingency table were >5; Fisher's exact test was used when cell counts in the 2 × 2 contingency table were ≤5. Continuous variables were compared between groups using the 2-sample independent t-test for normally distributed variables and the Wilcoxon rank sum test for data that were not normally distributed. For all comparisons, P < .05 was considered significant.

3 | RESULTS

3.1 | Animals and NSAIDs

A total of 62 dogs (27 Tufts University, 20 North Carolina State University, 9 University of Florida, 6 University of Pennsylvania, 0 Blue Pearl Pet Hospital) with complete medical records were treated with TPE as part of their NSAID overdose management and were included in our study. Thirty-six were males (28 castrated, 45.2%; 8 intact, 12.9%) and 26 were females (18 spayed, 29%; 8 intact, 12.9%), with a median age on presentation of 1.75 years (range, 2 months to

13.5 years). The most common breeds included 16 (25.8%) mixed breed dogs, 7 (11.3%) Labrador retrievers, 5 (8.1%) German shepherds, 4 (6.5%) American Staffordshire terriers, 4 (6.5%) Dachshunds, 3 (4.8%) Boston terriers, and 3 (4.8%) golden retrievers. Median body weight was 18.9 kg (range, 4.2-44.6 kg). On presentation, 24 (38.7%) dogs had clinical signs related to NSAID overdose. Twenty (32.3%) dogs had GI signs, 3 (4.8%) had evidence of AKI IRIS grade II (serum creatinine concentration of 1.7, 2.2 and 2.5 mg/dL) and 6 (9.7%) were presented with neurological signs. All dogs with evidence of AKI and 2 dogs with neurological signs also were presented with GI signs. Thirteen (65%) dogs with GI signs and 5 (83.3%) dogs with neurological signs had ingested ibuprofen.

The NSAIDs ingested were ibuprofen, naproxen, and carprofen in 29 (46.8%), 19 (30.6%), and 14 (22.6%) dogs, respectively. The median dose of ibuprofen, carprofen or naproxen ingested was 533 mg/kg (range, 36-4857 mg/kg), 217 mg/kg (range, 88-625 mg/kg) and 138 mg/kg (range, 26-3000 mg/kg), respectively. Two (3.2%), 14 (22.6%), and 46 (74.2%) dogs ingested a GI, renal, and neurological toxic dose. The median time elapsed between NSAID ingestion and presentation was 4 hours (range, 1-20 hours).

3.2 | Medical management

Emesis was induced with a standard dose of apomorphine (0.05-0.1 mg/kg) administered SC in 48 dogs. Emesis was successful in 45 (72.5%) dogs. A standard dose of activated charcoal (1-4 g/kg) was administered PO in 38 (62.3%) dogs. Thirty-four dogs received a repeat dose of charcoal: once in 14 cases (44.1%), twice in 11 cases (32.3%), 3 times in 1 case, 4 times in 4 cases, 5 times in 2 cases, and 6 times in 1 case. Medical management with a histamine H2-receptor antagonist, proton pump inhibitor, or prostaglandin E1 analog was given in 14 (22.6%), 45 (72.6%), and 45 (72.6%) dogs, respectively. All dogs received IV fluids during their hospitalization. Twenty-three (37.1%) dogs also received an IV infusion of lipid emulsion on admission while awaiting setup of the TPE session.

3.3 | Therapeutic plasma exchange

All dogs had a size-appropriate (range, 8 Fr × 12 cm to 14 Fr × 30 cm) double-lumen temporary hemodialysis catheter placed in an external jugular vein using the modified Seldinger technique while under sedation. Thirty-six (58%) TPE treatments were performed on a membrane-based platform and 26 (42%) treatments on a centrifuge-based platform. The mTPE sessions were performed on the Prismaflex platform (Gambro Lundia AB, Lund, Sweden), using a TPE 2000 circuit with a priming volume of 125 mL. The rate of replacement and duration of the mTPE session were based on a target filtration fraction of 15% to 20%. All mTPE dogs received systemic anticoagulation using unfractionated heparin (UFH) and were monitored by activated clotting time (ACT) to maintain the ACT within an acceptable range of 180 to 200 seconds. In 27 (75%) mTPE dogs, a constant rate infusion

(CRI) of calcium gluconate was used during the exchange with donor plasma to maintain a serum ionized calcium concentration >0.8 mmol/L. The cTPE sessions were performed on the Spectra Optia platform (Terumo BCT, Lakewood, Colorado) with a priming volume between 141 and 185 mL. All cTPE were performed using regional citrate anticoagulation (RCA) in accordance with the Spectra Optia operating system and a CRI of calcium gluconate to maintain serum ionized calcium concentration >0.8 mmol/L. Twenty (76.9%) cTPE dogs received systemic anticoagulation using UFH in addition to their RCA.

The median total replacement volume was 1300 mL (range, 220-3208 mL), which equated to a median of 1.6 plasma volumes (range, 0.4-2.2). This volume represented the amount needed to achieve an approximate 80% decrease in NSAID concentration.[28] The median donor plasma replacement volume was 500 mL (range, 0-2257 mL), representing a median of 50% (range, 0%-100%) of the volume replaced during TPE. In 32 dogs, the replacement fluid prescription also included a synthetic colloid. The median replacement volume consisted of 150 mL (range, 0-2305 mL) of colloid and 124 mL (range, 0-1500 mL) of crystalloids. The median duration of TPE sessions was 2.0 hours (range, 1.0-4.5 hours). Two cTPE sessions were performed on 2 consecutive days in 1 dog that ingested 400 mg/kg of carprofen. Despite having an approximate 80% toxin removal after the first session, a second session was performed at the attending clinician's discretion because of the concern for prolonged endogenous clearance at a toxic dose in comparison with the expected endogenous clearance at a therapeutic dose.

Patient adverse events were reported during 21 (33.8%) TPE sessions. During the exchange with donor plasma, 8 (12.9%) dogs developed urticaria with or without facial angioedema, 6 (9.6%) dogs developed a clinically relevant hypocalcemia without clinical signs, and 1 dog developed both urticaria and hypocalcemia. A significant increase in the occurrence of urticaria was noted during cTPE (7/26 [27%]) compared to mTPE (2/36 [6%]; $P = .03$) and was significantly associated with total plasma replacement volume ($P < .001$) and plasma replacement volume in relation to the patient's weight (mL/kg; $P = .04$). Half of the cTPE dogs and none of the mTPE dogs received a preventative dose of diphenhydramine before their TPE session ($P < .001$). Six of the 9 dogs with urticaria (66.6%) and 8 of the 53 dogs without urticaria (15.1%) had received a preventative dose of diphenhydramine ($P = .003$). Development of clinically relevant hypocalcemia did not differ between the 2 types of TPE ($P = .45$) and was not significantly associated with plasma replacement volume ($P = .43$) or plasma replacement volume in relation to the patient's weight ($P = .86$). Mild fluid-responsive hypotension was reported in 6 (9.6%) dogs and was not significantly associated with the type of TPE ($P = .39$). One dog developed both mild fluid-responsive hypotension and urticaria.

Eight (22.2%) of the 36 sessions performed on a membrane-based platform were complicated by circuit clotting, requiring circuit exchange in 5 cases, inability to return the blood at the end of the session in 2 cases, and interruption of the treatment 10 minutes before the end of the session in 1 case. No cTPE sessions were complicated by circuit clotting. Circuit clotting was significantly more frequent during mTPE (8/36 [22%]) than cTPE (0/26 [0%]; $P = .02$). Two of the 8 mTPE sessions discontinued because of circuit clotting resulted in

<1 plasma volume exchanged. One dog that ingested a maximum of 678 mg/kg of ibuprofen had only 0.4 plasma volume exchanged because of excessive transmembrane pressure at the beginning of the first session and a blood leak in the filter 15 minutes into the second session. The patient developed GI signs and IRIS grade III AKI (serum creatinine concentration 2.7 mg/dL) during hospitalization and was discharged after 6 days of hospitalization with a serum creatinine concentration of 1.9 mg/dL. The other patient ingested a maximum of 78 mg/kg of naproxen. Therapeutic plasma exchange was discontinued after 0.8 plasma volume exchanged because of severe patient hypotension and excessive transmembrane pressure in the circuit. The dog developed GI signs but no azotemia and was discharged after 2 days. Finally, 1 mTPE dog developed mild bleeding at the insertion site of the dialysis catheter.

3.4 | Outcome after TPE

Eleven (17.7%) dogs developed GI signs during hospitalization, in addition to the 20 dogs with GI signs on admission. Sixteen (25.8%) dogs developed AKI during hospitalization, in addition to the 3 dogs with AKI on admission. Only 1 of the 6 dogs with hypotension during TPE developed AKI during hospitalization. Eight (12.9%), 5 (8%), and 6 (9.6%) dogs had AKI classified as IRIS grade I, II and III, respectively. The median of the highest serum creatinine concentration during hospitalization was 1.1 mg/dL (range, 0.5-4.7 mg/dL). No dogs developed IRIS grade IV or V AKI (serum creatinine concentration >5 and >10 mg/dL, respectively). One of the 6 dogs that was presented with evidence of neurotoxicity had resolution of neurological signs during TPE. No dogs developed neurological signs after TPE that did not already have evidence of neurotoxicity at admission, and all dogs eventually recovered from their neurological signs after TPE. Thus, a total of 31 (50%), 19 (30.6%), and 5 (8%) dogs had evidence of GI, renal, and neurological toxicity during their hospitalization, respectively. After TPE, median total solids concentration decreased from 6.5 mg/dL (range, 4.4-8.5) on admission to 4.9 mg/dL (range, 3.8-7.4) at the time of discharge.

The median duration of hospitalization was 2.25 days (range, 1-11 days). The survival rate to discharge was 98.4%. A single dog in our cohort was euthanized 4 days after presentation. This dog ingested 400 mg/kg carprofen, had a first session initiated 3 hours after ingestion and received a second TPE session to remove any potential residual toxin, but subsequently developed a perforating ulcer and aspiration pneumonia. None of the discharged dogs were rehospitalized for the same problem. Thirty-one (91.2%) of the 34 dogs with at least 1 follow-up visit were not azotemic at the time of reevaluation. Two dogs that ingested a maximum of 1481 and 294 mg/kg of ibuprofen had serum creatinine concentrations of 1.8 and 2.0 mg/dL on reevaluation testing 1 week after discharge. One dog that ingested a maximum of 1357 mg/kg of ibuprofen had a serum creatinine concentration of 2.5 mg/dL 1 month after discharge. Of the 11 (17.7%) dogs with long term follow-up information after discharge, 10 (90.9%) were alive 1 year from the time of discharge.

4 | DISCUSSION

Our study describes a large population of dogs that ingested overdoses of 3 common NSAIDs managed with TPE. Specifically, the NSAIDs described were the veterinary prescription drug carprofen, and the 2 over-the-counter NSAIDs used in humans, ibuprofen and naproxen. The outcome for this cohort of dogs was excellent with an overall survival rate of 98.4%. When including clinical signs already present on admission, organ dysfunction developed frequently, with half of the dogs exhibiting GI signs and approximatively 33% developing AKI. Of the dogs described here, 74.2% ingested a large enough dose to lead to neurological toxicity, but only 8% experienced observable neurological signs during their hospitalization. Approximately half of the cases experienced TPE-associated complications, but all were temporary and reversible. Total plasma exchange is an effective therapeutic strategy for NSAID intoxication in dogs.

Our population selection was biased toward higher exposed NSAID doses because these dogs were more likely to have been treated with TPE. Most of our dogs had a severe overdose with approximatively 75% having potentially ingested a neurological toxic dose and another 22.6% a renal toxic dose. Furthermore, 30.6% of our population ingested naproxen, an NSAID with a lower toxic dose, lower clearance, and prolonged elimination half-life of 74 hours in dogs.

Patient adverse events were reported during 21 (33.8%) TPE sessions, but all were nonlife threatening and reversible. Evidence of urticaria was noted in 12% of dogs, presumably because of a type I hypersensitivity reaction to plasma administration. Most cases were adequately managed with administration of diphenhydramine. This complication potentially may have been avoided by preventative administration of diphenhydramine. However, urticaria was significantly more common in dogs that received preventative diphenhydramine than in those that did not ($P = .003$). Hypocalcemia occurred in approximatively 10% of dogs, secondary to citrate accumulation from blood product, RCA, or both. Iatrogenic hypocalcemia can be avoided when maximal citrate administration rates are maintained below 9.0 μmol/kg/min for dogs without kidney impairment.[18] At the time during TPE when a citrate-containing replacement solution is being administered, replacement fluid rates may need to be decreased. Additionally, titration of the calcium gluconate CRI may be necessary to avoid hypocalcemia. During cTPE with RCA, a CRI of calcium gluconate is used to maintain the serum ionized calcium concentration >0.8 mmol/L. The goal is to closely monitor the serum ionized calcium concentration to maintain it in the low reference range, because the calcium bound to citrate will be freed when the citrate is metabolized. In human medicine, the use of fresh frozen plasma has been associated with a higher rate of adverse reactions, urticaria and hypocalcemia being most commonly encountered.[29-31] In our dog population, urticaria was significantly associated with total plasma replacement volume and plasma replacement volume in relation to patient weight, but no association was found with hypocalcemia.

Circuit clotting was significantly more frequent during mTPE than cTPE. This finding is most likely related to the use of systemic anticoagulation and not RCA. Systemic anticoagulation with UFH is needed to prevent clotting in the extracorporeal circuit, but it should be used cautiously during mTPE to avoid complications (such as bleeding at the insertion site of the dialysis catheter, as seen in 1 of our patients). The anticoagulation prescription must achieve a fine balance between the risk of bleeding for the patient and the risk of clotting in the extracorporeal circuit. The ACT usually is maintained within an acceptable range of 180 to 200 seconds, but the degree of anticoagulation should be adapted to the transit time in the extracorporeal circuit, and patients with lower blood flow and prolonged transit time in the circuit require higher ACT. In cTPE, RCA results in chelation of calcium in the extracorporeal circuit and prevents clotting.[32] Also, the observed complications related to the donor plasma products (ie, hypersensitivity reaction, hypocalcemia secondary to stored citrate) could be avoided by selecting an alternative extracorporeal therapy such as hemoperfusion.[33,34] Hemoperfusion targets elimination of substances that have an affinity for activated carbons, thus purifying the patient plasma instead of discarding it, avoiding the need of replacement with donor plasma. Hemoperfusion also is associated with potential complications, the most common described being thrombocytopenia, hypocalcemia and hypoglycemia.[33,34]

Despite the high ingested dose reported, 43 (72.8%) of the dogs that were nonazotemic on presentation did not develop azotemia in-hospital and none of the dogs with AKI progressed to an IRIS grade IV or V AKI. One of the 6 dogs with evidence of neurotoxicity had resolution of the neurological signs during TPE. No dogs developed neurological signs after TPE that did not already have evidence of neurotoxicity at admission. With a median duration of hospitalization of 2.25 days (range, 1-11 days), TPE also potentially decreased the hospitalization time that could have been markedly prolonged if the patients had developed severe organ dysfunction. It also may have decreased the risk of life-threatening complications, as evidenced by the finding that only 1 of our patients died (from a perforating gastric ulcer and aspiration pneumonia). The survival to discharge rate of 98.4%, without rehospitalization, and 90.9% 1-year survival rate in our study are very promising.

Although our multicenter study aims to increase recognition of TPE as a safe treatment option for severe NSAID overdose in veterinary medicine, it had some limitations. The data used in our study reflects limitations encountered during management of dogs with a history of toxin ingestion. The time between ingestion and presentation frequently was based on an estimate. Because no point-of-care testing is available, the maximal dose reported was based on the owner's history that often included a wide dose range. Drug exposure may have been decreased by emesis after drug ingestion or after emesis induction. Twenty-three (37.1%) dogs also received alternative treatment with IV infusion of lipid emulsion while awaiting setup of the TPE session. Finally, calculation of drug clearance during the TPE session is not typically performed, and treatment efficacy in our study was based only on the development of clinical signs suspected to be secondary to the NSAID ingestion. Organ dysfunction associated with NSAID (e.g., GI erosions or ulcerations) may have been missed if it remained subclinical. Acute kidney injury also could have been underestimated because of the poor sensitivity of BUN and creatinine as markers of renal function.[35-38]

In conclusion, our study describes a TPE-treated population of dogs with excellent outcome despite exposure to high doses of NSAIDs. Half of the dogs experienced procedural adverse effects, specifically type I hypersensitivity, iatrogenic hypocalcemia, extracorporeal circuit clotting, and fluid-responsive hypotension. These adverse effects should be considered by attending clinicians, with awareness that close monitoring and early intervention should result in complete resolution of these complications. When TPE is available and the time frame is appropriate, this extracorporeal modality should be considered as an effective therapeutic option in cases of severe NSAID overdose.

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