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Case Series

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Intravenous lipid emulsion therapy in three cases of canine naproxen overdose

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Abstract

Objective – To report a case series of canine naproxen overdoses successfully treated with intravenous lipid emulsion therapy (IVLE).

Series Summary – Three dogs were presented for acute ingestion of naproxen and were treated with IVLE. Baseline and post treatment serum naproxen concentrations were measured. The first exposure involved ingestion of 61 mg/kg of an over-the-counter naproxen formulation in a 7-month-old male intact Labrador Retriever. Pre-IVLE toxin concentration assessed by high performance liquid chromatography (HPLC) was 73 μg/mL with a one-hour post-IVLE concentration decreasing to 30 μg/mL. The second and third exposures were 3-year-old female spayed Pembroke Welsh Corgi dogs from the same family, presented for potential ingestion of up to 207 mg/kg of a prescription strength naproxen formulation. Pre-IVLE naproxen concentration by HPLC for case 2 was 30 μg/mL with a reduction to 12 μg/mL and 7.2 μg/mL 1 and 3 hours post-IVLE treatment, respectively. For case 3, pre-IVLE naproxen concentration by HPLC was 86 μg/mL with post concentrations at 21 μg/mL one hour and 10 μg/mL 3 hours post-IVLE administration.

New or Unique Information Provided – Naproxen is a nonsteroidal anti-inflammatory drug with a long half-life and narrow margin of safety in dogs. Ingestion of > 5 mg/kg has been associated with adverse gastrointestinal effects, including ulceration. At doses > 10–25 mg/kg, acute kidney failure has been reported, and at doses > 50 mg/kg, neurologic abnormalities occur. This is the first reported use of IVLE for treatment of naproxen overdose with documented decrease in serum toxin concentrations shortly after administration. No long-standing gastrointestinal, renal, or neurologic effects occurred in these dogs.

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Keywords: Aleve, dog, intralipid, nonsteroidal anti-inflammatory drug, NSAID, toxicosis

Introduction

Naproxen is a propionic acid derivative nonsteroidal anti-inflammatory drug (NSAID) available over-the-counter and used for its anti-inflammatory, analgesic, and antipyretic properties in people.[1] Similar to other NSAIDs, it inhibits the enzyme cyclooxygenase (COX) with resultant disruption in prostaglandin synthesis.[2] Due to its long half-life in dogs of 74 hours, it has a narrow margin of safety and is not routinely used therapeutically in this species.[3] The main adverse effects associated with canine naproxen exposure reported by the ASPCA Animal Poison Control Center (APCC[a]) included, in decreasing frequency, vomiting, lethargy, anorexia, hematemesis, diarrhea, melena, and anemia. In dogs, oral ingestion of naproxen has been associated with gastrointestinal signs at dosages > 5 mg/kg, renal

Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
APCC	ASPCA Animal Poison Control Center
COX	cyclooxygenase
CRI	constant rate infusion
HPLC	high performance liquid chromatography
IVLE	intravenous lipid emulsion
LRS	lactated Ringer's solution
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NSAID	nonsteroidal anti-inflammatory drug
SQ	subcutaneously

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damage at dosages > 10–15 mg/kg, and neurologic abnormalities at dosages > 50 mg/kg (APCC).

Treatment for acute toxicosis has been limited to supportive measures, including IV fluid therapy, antiemetics, gastric protectants, use of prostaglandin analogs (eg, misoprostol), and cholestyramine, a bile acid sequestrant.[4] However, despite these measures, serious morbidity and mortality associated with this intoxication have been described in the literature.[5–7] Recently, successful use of intravenous lipid emulsion therapy (IVLE) was described for a case of ibuprofen toxicosis in a dog.[8] As naproxen is structurally and pharmacologically similar to ibuprofen and has high lipid solubility, use of a lipid infusion as adjunct therapy for this intoxication was investigated.

IVLE protocol

The administration of the IVLE therapy (Intralipid 20%[b]) was consistent across all cases in this report. The product was administered through a nondesignated peripheral catheter without the use of a filter. Monitoring during infusion consisted of assessment of mentation, temperature, pulse, and respiration every 5 minutes for the first 15 minutes, then every 15 minutes until completion.

Case Series

Case 1

A 7-month-old, 35.9 kg, intact male Labrador Retriever dog presented for potential ingestion of 61 mg/kg of an over-the-counter naproxen formulation[c] designed for use in people. The exposure was accidental and occurred within 3 hours of presentation, with up to 10 liquid gel capsules (220 mg/capsule) reportedly ingested. The patient had no pertinent prior medical concerns.

On presentation, the patient was bright, alert, and responsive with a normal heart rate of 90/min, respiratory rate of 28/min, and temperature of 38.9°C (102.0°F). Systolic blood pressure by indirect Doppler measurement was 110 mm Hg. Electrocardiogram revealed a normal sinus rhythm. Physical examination was unremarkable.

Emesis was induced with apomorphine[d] (1.4 mg; 0.04 mg/kg IV) and the patient vomited digested food with small pieces of plastic and no obvious medications. Standard treatment for NSAID ingestion, including IV fluid diuresis, activated charcoal, and gastrointestinal protection was advised by the APCC. An IV catheter[e] was placed and the patient was administered lactated Ringer's solution[f] (LRS) IV at 200 mL/h (5.6 mL/kg/h). Dolasetron[g] (28.7 mg; 0.8 mg/kg IV) was administered prior to administration of activated charcoal. Initially, 400 mL (1.1 g/kg) activated charcoal with sorbitol[h] were administered orally; a second, reduced dose of activated charcoal without sorbitol[i] was administered 8 hours later (200 mL; 0.58 g/kg). Other immediate treatments included sucralfate[j] (1 g PO q 6 h), omeprazole[k] (20 mg; 0.56 mg/kg PO q 24 h), and S-adenosyl-methionine[l] (675 mg PO q 24 h).

A venous blood gas and electrolyte point-of-care blood profile[m] revealed a mildly increased bicarbonate concentration (mild metabolic alkalosis; Table 1). Serum biochemical panel revealed mild hyperphosphatemia and mild increase in alanine aminotransferase (ALT) activity. Complete blood count and urinalysis were unremarkable. Serum was stored frozen at –20°F for naproxen concentration measurement by HPLC.

Due to the potential for a large naproxen overdose in this case, IVLE was administered at 2 mL/kg over 15 minutes, followed by a constant rate infusion (CRI) of 0.25 mL/kg/min over 30 minutes. Serum was collected and frozen at –20°F one hour after the lipid infusion for posttreatment naproxen concentration by HPLC. Marked gross lipemia was present post-IVLE. No other adverse events were noted. Pre-IVLE serum naproxen concentration was 73 μg/mL and 1-hour post-IVLE concentration was 30 μg/mL (Table 2).

The patient was admitted to the ICU for supportive treatments and fluids. Daily point-of-care blood profiles assessed kidney function and a full serum biochemical panel was performed 72 hours after presentation. At that time, moderate azotemia, mild hyperproteinemia, mild hypochloremia, hyperglycemia, and increased ALT activity were observed (Table 1). A urinary catheter was placed to monitor urine output and help guide fluid therapy. Fluid rate was adjusted to 250 mL/h (7 mL/kg/h IV) for ongoing diuresis. Azotemia resolved after an additional 24 hours of fluid therapy. Recheck blood work at that time revealed a mild anemia, hypoproteinemia, and mild hyperphosphatemia. These findings, in conjunction with an increased BUN/creatinine ratio, raised concern for occult gastro-intestinal bleeding.

The patient remained hospitalized for 96 hours of therapy and was discharged with omeprazole, sucralfate, and S-adenosyl-methionine for 7 days. One-week follow-up revealed a persistent mild increase in ALT activity with continued resolution of the azotemia and other values unremarkable. The patient was clinically normal at last follow-up, 10 months postnaproxen ingestion with no further bloodwork available.

Cases 2 and 3

Two 3-year-old spayed female Pembroke Welsh Corgi dogs presented for possible accidental ingestion of up to 5 tablets (500 mg/tablet) of a prescription strength

Table 1: Pertinent laboratory results at presentation and during treatment for Case 1

	Presentation	24 hours	48 hours	72 hours	96 hours	Day 11	Reference interval
BUN, mmol/L (mg/dL)	7.5 (21)	3 (8)	3.5(10)	22 (61)	2 (6)	3.5 (10)	0.2–10.7 mmol/L (6–30 mg/dL)
Creat, μmol/L (mg/dL)	80 (0.9)	71 (0.8)	71 (0.8)	168 (1.9)	44 (0.5)	44 (0.5)	44–133 μmol/L (0.5–1.5 mg/dL)
USG	1.056	—	—	—	—	—	Concentrated ≥1.030
TP, g/L (g/dL)	61 (6.1)	56 (5.6)	—	71 (7.1)	49 (4.9)	60 (6.0)	51–70 g/L (5.1–7.0 g/dL)
Phos, mmol/L (mg/dL)	2.1 (6.4)	—	—	1.4 (4.2)	1.7 (5.3)	1.7 (5.2)	0.9–1.7 mmol/L (2.7–5.2 mg/dL)
K, mmol/L (mEq/L)	4.6 (4.6)	4.35 (4.35)	4.66 (4.66)	3.6 (3.6)	4.1 (4.1)	4.0 (4.0)	3.9–5.5 mmol/L (3.9–5.5 mEq/L)
Cl, mmol/L (mEq/L)	109 (109)	113.1 (113.1)	111 (111)	99 (99)	114 (114)	112 (112)	107–118 mmol/L (107–118 mEq/L)
Glu, mmol/L (mg/dL)	5.7 (104)	5.7 (104)	6.2 (112)	9.9 (180)	6.2 (113)	6.1 (110)	3.7–6.9 mmol/L (68–126 mg/dL)
ALT, U/L (units/L)	71 (71)	—	—	104 (104)	—	82 (82)	8–65 U/L (8–65 units/L)
HCO_3 mmol/L (mEq/L)	26 (26)	23.5 (23.5)	27.5 (27.5)	18.4 (18.4)	19.8 (19.8)	23.1 (23.1)	16–24 mmol/L (16–24 mEq/L)
PCV,%	41	42	—	35	32	38	35–52%

BUN, blood urea nitrogen; Creat, creatinine; USG, urine-specific gravity; TP, total protein; Phos, phosphorous; K, potassium; Cl, chloride; Glu, glucose; ALT, alanine aminotransferase; HCO_3, bicarbonate; PCV, packed cell volume.

Table 2: Serum naproxen concentrations by HPLC prior and 1 and 3 hours following treatment with IVLE therapy

	Prior, μg/dL	1 hour post, μg/dL	3 hours post, μg/dL
Case 1	73	30	—
Case 2	30	12	7.2
Case 3	86	21	10

naproxen formulation,[n] for a possible dose exposure of up to 207 mg/kg orally.

Case 2

On presentation, the patient was bright, alert and responsive, and panting, with a heart rate of 128/min, normal temperature of 38.8°C (101.8°F), and a body weight of 15.1 kg. Systolic indirect blood pressure was 120 mm Hg via Doppler and electrocardiogram revealed a normal sinus rhythm. Physical examination was unremarkable.

Emesis was induced with apomorphine (0.45 mg; 0.03 mg/kg IV) and consisted of brown liquid and food with no obvious medications. Maropitant[o] was then administered (15 mg; 1 mg/kg SQ [subcutaneously]) for its antiemetic and anti-nausea effects. The APCC was consulted for both dogs and recommendations were similar to those for Case 1. An IV catheter was placed and IV fluid diuresis was initiated at 75 mL/h LRS (5 mL/kg/h). Activated charcoal was administered orally, initially with sorbitol (166 mL; 1.1 g/kg) and then without sorbitol at a half dose (83 mL; 0.57 g/kg PO q 8 h) for 2 doses. Sucralfate (0.5 g PO q 6 h) and famotidine[p] (7.6 mg; 0.5 mg/kg IV q 12 h) were started.

Complete blood count revealed a mildly low mean corpuscular hemoglobin concentration (MCHC), slightly decreased monocytes and few echinocytes. Serum biochemical profile revealed increased alkaline phosphatase (ALP) and ALT activities (Table 3). Urinalysis and point-of-care blood profile were unremarkable. Serum was stored frozen at –20°F for naproxen concentration testing by HPLC. Due to the mild increases in liver enzyme activities, S-adenosyl-methionine, and silybin medication[q] (225 mg PO q 24 h) was added to the treatment regime.

The high level of potential naproxen exposure prompted the decision to administer IVLE therapy. The patient received 1.5 mL/kg IV over 15 minutes followed by 0.31 mL/kg/min CRI over 1 hour. Serum was collected and frozen at –20°F 1 hour and 3 hours after IVLE for posttreatment naproxen concentrations by HPLC. Marked gross lipemia was present post-IVLE. No other adverse events were noted. The pre-IVLE serum naproxen concentration was 30 μg/mL, and post-IVLE concentrations of 12 μg/mL and 7.2 μg/mL were reported at 1 and 3 hours, respectively (Table 2).

The patient was admitted to the ICU for fluid diuresis and supportive care. Daily point-of-care blood profiles assessed kidney function with no azotemia observed throughout hospitalization. Persistent increase in the liver enzyme activities were observed, with an increase in ALP and ALT activities at 24 hours, and improvement of ALT but worsening of ALP by 48 hours. There was mild hypokalemia, mild hyperphosphatemia,

Table 3: Pertinent laboratory results at presentation and during treatment for Case 2

	Presentation	24 hours	48 hours	72 hours	Day 11	Reference interval
BUN, mmol/L (mg/dL)	7 (19)	3 (9)	4.5 (13)	5.5 (16)	5.5 (16)	0.2–10.7 mmol/L (6–30 mg/dL)
Creat, μmol/L (mg/dL)	88 (1.0)	80 (0.9)	80 (0.9)	88 (1.0)	88 (1.0)	44–133 μmol/L (0.5–1.5 mg/dL)
USG	1.021	1.008	1.010	—	—	Concentrated ≥1.030
TP, g/L (g/dL)	56 (5.6)	48 (4.8)	52 (5.2)	—	57 (5.7)	51–70 g/L (5.1–7.0 g/dL)
Phos, mmol/L (mg/dL)	1.2 (3.7)	2 (6.2)	0.97 (3.0)	—	1.23 (3.8)	0.9–1.7 mmol/L (2.7–5.2 mg/dL)
K, mmol/L (mEq/L)	4.8 (4.8)	3.62 (3.62)	3.9 (3.9)	4.38 (4.38)	4.3 (4.3)	3.9–5.5 mmol/L (3.9–5.5 mEq/L)
ALP, U/L (units/L)	(105)	(142)	(183)	—	(186)	7–92 U/L (7–92 units/L)
ALT, U/L (units/L)	95 (95)	142 (142)	91 (91)	—	65 (65)	8–65 U/L (8–65 units/L)
Trig, mmol/L (mg/dL)	6 (52)	85 (754)	5.65 (50)	—	11.6 (103)	3.6–17.4 mmol/L (32–154 mg/dL)
MCHC, g/L (g/dL)	319 (31.9)	—	—	—	—	320–360 g/L (32–36 g/dL)
PCV,%	52	52	—	54	—	35–52%
HCO_3, mmol/L (mEq/L)	18.6 (18.6)	17.2 (17.2)	—	19.0 (19.0)	27 (27)	16–24 mmol/L (16–24 mEq/L)

BUN, blood urea nitrogen; Creat, creatinine; USG, urine-specific gravity; TP, total protein; Phos, phosphorous; K, potassium; ALP, alkaline phosphatase; ALT, alanine aminotransferase; Trig, triglycerides; MCHC, mean corpuscular hemoglobin concentration; PCV, packed cell volume; HCO_3, bicarbonate.

severe hypertriglyceridemia, and mild hypoproteinemia at 24 hours that resolved by 48 hours. Urinalysis at 72 hours revealed mild proteinuria and glucosuria. Other laboratory parameters were within reference intervals (Table 3).

During hospitalization, the patient remained asymptomatic with no reported complications. Discharge occurred at 72 hours, with S-adenosyl-methionine and silybin medication (225 mg PO q 24 h) and sucralfate 0.5 g PO q 8 h) for 7 days. A follow-up serum biochemical panel one week after discharge revealed increased ALP activity and elevated bicarbonate concentration (mild metabolic alkalosis). On urinalysis, a specific gravity of 1.020, pH 8.5, and mild proteinuria were reported (Table 3). She was asymptomatic on recheck 2 months after naproxen ingestion with no additional bloodwork available.

Case 3

On presentation, the patient was bright, alert and responsive, panting with a heart rate of 120/min, a temperature of 38.4°C (101.1°F), and a body weight of 12.1 kg. Systolic indirect blood pressure was 110 mm Hg via Doppler and electrocardiogram revealed a normal sinus rhythm. Physical examination was unremarkable.

Emesis was induced with apomorphine (0.36 mg; 0.03 mg/kg IV), and vomitus consisted of brown liquid and food without obvious medications. Maropitant was then administered (12 mg; 1 mg/kg SQ) and an IV catheter was placed for IV LRS fluid diuresis at 60 mL/h (5 mL/kg/h). Activated charcoal was administered orally, initially with sorbitol (133 mL; 1.1 g/kg PO) and then without sorbitol at a half dose (67 mL; 0.58 g/kg PO q 8 h) for 2 doses. Sucralfate (0.5 g PO q 6 h) and famotidine (6 mg; 0.5 mg/kg IV q 12 h) were started.

Complete blood count revealed a mildly increased mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mildly low monocytes, eosinophilia, few echinocytes, and rare polychromasia. Serum biochemical panel and point-of-care blood profile were unremarkable. Urinalysis by cystocentesis revealed a specific gravity of 1.068, pH 7, mild proteinuria, trace blood, bilirubinuria, struvite crystalluria, and rare epithelial cells and granular casts (Table 4). Serum was stored frozen at –20°F for naproxen concentration testing by HPLC.

Due to the potentially high drug exposure, IVLE was initiated at 1.5 mL/kg IV over 15 minutes followed by 0.25 mL/kg/min CRI over 1 hour. Serum was collected and frozen at –20°F 1 hour and 3 hours after the lipid infusion for posttreatment naproxen concentrations by HPLC. Marked gross lipemia was present post-IVLE. No other adverse events were noted. Pre-IVLE serum naproxen concentration was 86 μg/mL, with 1 hour and 3 hour post-IVLE treatment serum concentrations reported at 21 μg/mL and 10 μg/mL, respectively (Table 2).

Table 4: Pertinent laboratory results at presentation and during treatment for Case 3

	Presentation	24 hours	48 hours	72 hours	96 hours	Day 11	Reference interval
BUN, mmol/L (mg/dL)	10.5 (29)	3 (9)	8 (23)	3.5 (10)	3.5 (10)	5.5 (16)	0.2–10.7 mmol/L (6–30 mg/dL)
Creat, μmol/L (mg/dL)	97 (1.1)	88 (1.0)	80 (0.9)	71 (0.8)	71 (0.8)	88 (1.0)	44–133 μmol/L (05–1.5 mg/dL)
USG	1.068	—	1.040	—	—	—	Concentrated ≥1.030
TP, g/L (g/dL)	53 (5.3)	—	36 (3.6)	—	43 (4.3)	54 (5.4)	51–70 g/L (5.1–7.0 g/dL)
Na, mmol/L (mEq/L)	147 (147)	144.5 (144.5)	139 (139)	145.8 (145.8)	145 (145)	146 (146)	141–152 mmol/L (141–152 mEq/L)
K, mmol/L (mEq/L)	4.5 (4.5)	3.83 (3.83)	4.1 (4.1)	3.69 (3.69)	4.4 (4.4)	3.9 (3.9)	3.9–5.5 mmol/L (3.9–5.5 mEq/L)
iMg, mmol/L	0.50	0.36	—	0.37	—	—	0.47–0.62 mmol/L
Alb, g/L (g/dL)	30 (3.0)	—	19 (1.9)	—	19(1.9)	21 (2.1)	25–38 g/L (2.5–3.8 g/dL)
MCV, fl/cell	79.3	—	—	—	79.2	—	60–77 fl/cell
MCH, pg/cell	25.6	—	—	—	25.5	—	20–25 pg/cell
PCV,%	48	45	-	50	48	—	35–52%
Chol, mmol/L (mg/dL)	6.37 (246)	—	6.4 (247)	—	6.09 (235)	7.98 (308)	3.34–7.69 mmol/L (129–297 mg/dL)

BUN, blood urea nitrogen; Creat, creatinine; USG, urine-specific gravity; TP, total protein; Na, sodium; K, potassium; iMg, ionized magnesium; Alb, albumin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PCV, packed cell volume; Chol, cholesterol.

The patient was admitted to the ICU for IV fluid diuresis and supportive care. Daily point-of-care blood profiles assessed kidney function, which remained normal throughout hospitalization. Mild hyponatremia developed at 48 hours and resolved without treatment by the time of discharge. There were persistent mild hypomagnesemia, hypoproteinemia, hypoalbuminemia, and mildly increased ALP activity at 96 hours. Mild hypokalemia was noted at 24 hours and 72 hours, and resolved by 96 hours. On the CBC at 96 hours, MCV and MCH were still mildly increased with polychromasia and echinocytes observed. Urinalysis repeated at 96 hours revealed proteinuria, glucosuria, rare epithelial cells, and granular casts. Other bloodwork parameters were within reference intervals (Table 4).

Melena developed at 72 hours, prompting the addition of metronidazole^{r} (125 mg; 10 mg/kg PO q 12 h). The patient otherwise remained asymptomatic during hospitalization. Melena resolved and the patient was discharged at 96 hours with sucralfate (0.5 g PO q 8 h) and metronidazole as above for 7 days. Follow-up was performed one week after discharge, and a serum biochemical panel revealed mild hypoalbuminemia and hypercholesterolemia. Urinalysis was unremarkable (Table 4). She was asymptomatic 2 months after naproxen ingestion with no additional bloodwork available.

Discussion

The use of IVLE in the treatment of naproxen overdose has been postulated to be effective at increasing the rate of drug elimination and decreasing adverse effects.[9] To the authors' knowledge, this case series is the first documented use of IVLE in clinical patients for naproxen overdose.

NSAID exposure is commonly reported to the APCC, and accounts for approximately 3% of their total caseload.[2] Naproxen is reportedly the third most commonly ingested NSAID, with ibuprofen and aspirin ranking first and second, respectively.[10] Naproxen is used commonly in people, with various formulations and concentrations available over-the-counter and by prescription.

Naproxen is a propionic acid derivative having analgesic, anti-inflammatory, and antipyretic activity. Such activity is thought to be mediated by inhibition of the COX enzymes with consequent reduction in the synthesis of prostaglandins. By inhibiting formation of thromboxane A2, it also inhibits platelet aggregation. Naproxen is a nonselective COX inhibitor, affecting COX 1 and COX 2. The constitutively produced COX enzyme (COX 1) helps maintain gastric mucosal integrity, renal perfusion, and glomerular filtration, whereas the inducible COX enzyme (COX 2) is expressed in macrophages and other cells at sites of inflammation.[11] Nonselective inhibition of COX lends to more gastrointestinal and renal effects.

In Case 1 of this report, azotemia developed after 72 hours of IV fluid therapy, and resolved 24 hours later. This may have been a prerenal azotemia from dehydration or inadequate fluid intake. Alternatively, acute kidney injury may have developed due to

inhibition of prostaglandin synthesis and exaggeration of renal hypoperfusion and vasoconstriction. Hydration was assessed in this case through serial body weight measurements and monitoring of physical examination parameters. An indwelling urinary catheter was placed to quantify urine output relative to fluid intake only after azotemia developed. Proteinuria was noted in both Corgis in this report and Case 3 had granular casts. Mild proteinuria persisted in Case 2 with resolution of proteinuria and casts in Case 3 at the one-week follow-up period. Both dogs were asymptomatic at that follow up.

Naproxen has a narrow margin of safety in dogs. Its oral absorption is rapid with peak plasma concentrations achieved in 0.5–3 hours. It has extensive enterohepatic circulation, resulting in a long half-life. The drug is highly protein bound (>90%) and is primarily eliminated through the bile in dogs, with an oral bioavailability of 68–100%.[12] In Case 1, ingestion of a single 220 mg liquid gel would have exceeded the gastro-intestinal toxic dose. For Cases 2 and 3, a single 500 mg tablet would have exceeded the renal toxic dose.

Several case reports of naproxen intoxication have been described in the veterinary literature with commonly reported side effects including vomiting, melena, abdominal pain, weakness, ataxia, and depression.[5,6,7,13,14] Treatment has been limited to supportive care, with APCC recommendations for decontamination with emesis and activated charcoal, IV fluid diuresis, gastrointestinal protectants, and clinicopathologic monitoring. Although not standard of care in veterinary medicine, IVLE has been successful in the treatment of various toxicoses, including calcium channel blockers, beta blockers, and tricyclic antidepressants in people and animals,[15–18] and more recently for lidocaine toxicosis in a cat,[19] and moxidectin[20] and ibuprofen[8] intoxications in dogs.

IVLEs have antidotal effects that vary with the lipophilicity of the toxic agent: the more lipophilic the agent, the more helpful IVLE is likely to be.[9] Their mechanism of action of IVLE is probably at least partially due to a "lipid sink" effect, wherein the toxic agent is sequestered in a lipid compartment within the intravascular space and then eliminated.[9] The lipophilicity of a drug and thus its solubility and extent of distribution determine its log *P* value, where *P* represents the partition coefficient. The higher the log *P* value, the more lipophilic the drug, with values >1 representing lipid soluble agents. The log *P* of naproxen is 3.18, correlating to high lipophilicity. In the cases reported here, the post-IVLE therapy naproxen concentrations were not immeasurably low. There are a number of possible reasons for this observation. Firstly, the timing of IVLE, being given 3 hours after presentation in Case 1 and 1 hour after presentation in Cases 2 and 3, may have affected drug detoxification. In all cases, time between ingestion and presentation for care may have been as long as 3 hours in Case 1 and 4 hours in Cases 2 and 3. It is possible that absorption of the drug during these time delays affected the efficacy of IVLE treatment. It is possible that ongoing enterohepatic circulation might have contributed to the still measurable naproxen concentrations following IVLE therapy. Lastly, the dose of IVLE administered may not have been sufficient to completely eliminate the drug. The recommended dose range for IVLE has been reported to be 1.5–4 mL/kg IV bolus over 15 minutes, followed by a CRI of 0.25–0.5 mL/kg/min for one hour.[18–20] Although all of these patients received IVLE within this dosing range, it is possible that administering a higher or repeated dose of IVLE would have further reduced the naproxen concentrations. Serum naproxen concentrations were not available during case management, so clinicians were unaware that toxin remained in animals that appeared clinically normal at the time.

We are proposing that IVLE was responsible for the rapid rate of reduction in serum naproxen concentrations seen in these 3 patients. All lipid therapy was given after routine decontamination and initiation of supportive medications. Pre-IVLE serum samples were taken immediately prior to IVLE administration and 1 hour (Case 1) or 1 and 3 hours (Cases 2 and 3) post-IVLE therapy. Aside from continued IV fluid therapy during the 1 and 3 hour time periods, no other interventions were initiated during this interval that could have affected the results. Additionally, because naproxen has a long half-life in dogs of up to 74 hours, drug concentrations would not have been expected to decline to the concentrations reported after 1–3 hours. However, it is difficult to know if IVLE treatment prevented clinical complications or affected outcome compared to standard decontamination methods in these dogs. Serum naproxen concentrations were not measured at similar times after standard decontamination methods alone, which could have provided control population data. Further study in this area may be warranted to compare current decontamination recommendations alone to those paired with IVLE treatment.

IVLE has been associated with adverse events, including microbial contamination of the product, acute pyrogenic reactions,[21] delayed or subacute reactions,[21] neurologic complications,[22] alterations in pulmonary function,[23,24] hypertriglyceridemia and lipemia,[25] and fat overload syndrome.[26] Fat overload syndrome is characterized by fat embolism, coagulopathy, hepatosplenomegaly, icterus, and hemolysis.[26] Due to these potential adverse effects, IVLE should not supersede effective traditional therapies for drug toxicoses. Lipid therapy should instead be considered an adjunct treatment for ingestion of lipophilic drugs in doses that may do considerable harm.

In this case series, 3 dogs having ingested large doses of naproxen were successfully treated with IVLE without complications noted secondary to its administration. Serum naproxen concentrations in all dogs were reduced after lipid therapy. All dogs were all discharged from the hospital within 72–96 hours of treatment without adverse gastrointestinal or persistent renal effects.

Footnotes

[a] APCC Animal Poison Control Center electronic medical record database.
[b] Intralipid 20%. Baxter Healthcare, Deerfield, IL.
[c] Aleve, Liquid Gels. Bayer Corporation, Pittsburgh, PA.
[d] Apomorphine, Medisca, Plattsburgh, NY.
[e] Venocath 18g. Hospira, Inc., Lake Forest, IL.
[f] Lactated Ringer's Solution. Abbott Laboratories, North Chicago, IL.
[g] Dolasetron. Sanofi-aventis, Bridgewater, NJ.
[h] Toxiban (Charcoal-Kaolin with Sorbitol). Lloyd, Inc., Shenandoah, IA.
[i] Toxiban (Charcoal-Kaolin). Lloyd, Inc.
[j] Sucralfate. Nostrum Laboratories, Kansas City, MO.
[k] Omeprazole. Sunmark, San Francisco, CA.
[l] S-adenosylmethionine. Nutramax Laboratories, Inc., Edgewood, MD.
[m] Critical Care Xpress. NOVA Biomedical, Waltham, MA.
[n] Naproxen EC. Novartis Corporation (Sandoz Generics), East Hanover, NJ.
[o] Maropitant. Pfizer Animal Health, New York, NY.
[p] Famotidine. APP Pharmaceuticals, Schaumberg, IL.
[q] Denamarin. Nutramax Laboratories, Inc, Edgewood, MD.
[r] Metronidazole. Teva Pharmaceuticals, Sellersville, PA.

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