JOURNAL OF
Veterinary Emergency
AND Critical Care

Case Report

Journal of Veterinary Emergency and Critical Care **26**(6) 2016, pp 787–792
doi: 10.1111/vec.12544

Treatment of ibuprofen toxicity with serial charcoal hemoperfusion and hemodialysis in a dog

Barbara S. Tauk, DVM, DACVIM and Jonathan D. Foster, VMD, DACVIM

Abstract

Objective – To describe the efficacy of serial charcoal hemoperfusion and hemodialysis in removing ibuprofen from a dog with severe clinical signs of toxicity.
Case Summary – A dog ingested a minimum of 2,200 mg/kg of ibuprofen resulting in progressive neurologic dysfunction that progressed to a comatose state by the time of presentation. Extracorporeal charcoal hemoperfusion coupled serially with hemodialysis was performed to remove ibuprofen from this patient. Serial charcoal hemoperfusion and hemodialysis therapy resulted in complete reversal of the neurologic dysfunction in this dog. No evidence of acute kidney or hepatic injury was observed. Serum ibuprofen concentrations confirmed the efficacy of this treatment.
New Information Provided – This report details the technique for extracorporeal extraction of ibuprofen, a methodology that could be employed for other toxicities due to substances with similar pharmacokinetics. Complications and limitations (eg, saturation of the charcoal cartridge) of the therapy are discussed.

(J Vet Emerg Crit Care 2016; 26(6): 787–792) doi: 10.1111/vec.12544

Keywords: canine, dialysis, extracorporeal therapy, toxicology

Abbreviation

RI reference interval

Case Summary

A 15-month-old neutered male German Shepherd mixed-breed dog, weighing 23 kg, was referred for acute neurologic signs following ingestion of a minimum of 2,200 mg/kg of ibuprofen.[a] Within an hour following ingestion, the dog began to vomit at home; however, no intact pills were seen in the vomitus. The dog was taken to his primary care veterinarian where an unknown dose of apomorphine was administered to induce vomiting, which was unsuccessful. No other therapies were performed by the primary care veterinarian. Within an hour after the suspected time of ingestion, the dog became ataxic and his mentation became progressively obtunded. The dog was then referred for extracorporeal drug removal. Upon presentation to the referral hospital the dog was comatose, although still maintaining adequate ventilation, which was determined by a venous blood gas measurement,[b] which revealed an appropriate $PvCO_2$ (34.2 mm Hg; reference interval [RI], 35–45 mm Hg). On examination the dog was hypothermic 37.7°C (99.9°F); had fixed miotic pupils; lacked response to noxious stimuli; and had absent gag, palpebral, and pupillary light reflexes. The venous blood gas measurement revealed hyperlactatemia (6.7 mmol/L, RI, < 2 mmol/L) and acidemia (pH 7.27, RI, 7.35–7.45). Serum biochemistry profile results revealed hypoalbuminemia (20.0 g/L [2.0 g/dL]; RR: 25.0-27.0 g/L [2.5-3.7 g/dL]), hypoglobulinemia (20.0 g/L [2.0 g/dL]; RR, 24.0–40.0 g/L [2.4–4.0 g/dL]), mild hyperglycemia (8.6 mmol/L [155 mg/dL], RI, 3.6–6.2 mmol/L [65–112 mg/dL]), and normal renal and liver parameters (alanine transferase [ALT], 65 U/L; RI, 16–91 U/L), creatinine (141.4 μmol/L [1.6 mg/dL]; RI, 61.9–159.1 μmol/L [0.7-1.8 mg/dL]), and blood urea nitrogen (BUN) (4.3 mmol/L [12 mg/dL]; RI, 1.8–10.7 mmol/L [5–30 mg/dL]). The packed cell volume was 40% and total plasma protein was 40.0 g/L (4.0

From the Department of Clinical Studies, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104.

Offprints are not available from the authors.

The authors declare no conflict of interests.

Presented as a poster at the Advanced Renal Therapies Symposium, New York, NY, March 26–29, 2014.

Address correspondence and reprint requests to
Dr. Jonathan D. Foster, Friendship Hospital for Animals, 4105 Brandywine St, Washington DC, 20016, USA.
Email: jdfoster@friendshiphospital.com
Submitted November 24, 2014; Accepted April 22, 2015.

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g/dL). The panhypoproteinemia was suspected to be due to blood loss from gastric ulceration. A urinalysis was not performed.

The dog was immediately intubated without sedation and gastric lavage was attempted but unsuccessful. A 500 mL bolus of PlasmaLyte A[c] was administered intravenously to help improve tissue perfusion and hyperlactatemia. A dual-lumen dialysis catheter[d] was placed in the right jugular vein percutaneously using a modified Seldinger technique, without sedation. A 6-hour extracorporeal treatment of charcoal hemoperfusion coupled serially with a conventional dialyzer was then performed using an intermittent hemodialysis machine.[e] An extracorporeal circuit was constructed utilizing a blood tubing set,[f] a charcoal cartridge,[g] and a hemodialyzer[h] (Figure 1). The total extracorporeal blood volume totaled 210 mL. Three hours into the treatment the charcoal cartridge was replaced. The total volume of blood processed during the 6-hour treatment was 34.5 L (1.5 L/kg).

At the start of the combination charcoal hemoperfusion and hemodialysis treatment, the dog was comatose and hypotensive on indirect measurement (systolic 60 mm Hg, diastolic 40 mm Hg, mean 40 mm Hg). The hypotension was treated with a 10 mL/kg PlasmaLyte A bolus and a 2 mL/kg hydroxyethyl starch[i] bolus that improved the hypotension (systolic 105 mm Hg, diastolic 61 mm Hg). He was intubated, but did not need any assisted ventilation. Approximately 2 hours into therapy, the dog became more alert, was able to raise his head, and had a palpebral and pupillary light reflex. Approximately 3 hours into treatment, the dog regained gag and swallow reflexes, was able to be extubated, and began to sit sternally. He remained bright, alert, and responsive for the rest of the treatment. At the completion of treatment, the patient was neurologically appropriate and able to walk. Following correction of the dog's hypotension (systolic 116 mm Hg, diastolic 65 mm Hg), a 0.75 g/kg dose of mannitol[j] was administered 90 minutes into therapy for renoprotection. A second 0.25 g/kg dose was administered at the end of treatment. No evidence of dialysis disequilibrium syndrome was appreciated.

Starting at the onset of extracorporeal therapy and approximately hourly after starting treatment, serum for ibuprofen concentrations was obtained from the arterial port of the extracorporeal circuit. Two milliliters of whole blood was removed for each analysis; samples were also obtained postcharcoal (predialyzer) and postdialyzer (see Figure 1). Blood samples were also drawn for ibuprofen measurement 12, 24, and 36 hours post completion of extracorporeal therapy (Figure 2 and Table 1). Ibuprofen concentration was determined by high-performance liquid chromatography.[k] The blood samples obtained post charcoal cartridge (extracorporeal blood that had passed through the charcoal cartridge) demonstrated likely saturation of the cartridge after 2 hours of hemoperfusion. Times when the postcharcoal samples had a higher concentration than precharcoal (as with postdialyzer compared to postcharcoal/predialyzer) suggests that ibuprofen is likely leaching out of the device due to saturation. Blood samples obtained predialyzer (postcharcoal) and postdialyzer were evaluated to determine the contribution the hemodialyzer played in ibuprofen extraction. The hemodialyzer had negligible effects on the extraction of ibuprofen; average concentration postdialyzer was 8% higher than concurrent predialyzer samples. This change in ibuprofen concentration across the dialyzer ranged between a 52% increase and 34% reduction.

After completion of extracorporeal therapy, the dog was hospitalized for 4 days. The dog was treated with PlasmaLyte A (23 mL/kg/day), hydroxyethyl starch (23 mL/kg/day), misoprostol[l] (4.3 μg/kg PO q 6 h), esomeprazole[m] (0.5 mg/kg IV q 24 h), ondansetron[n] (0.2 mg/kg IV q 8 h), metronidazole[o] (10 mg/kg PO q 12 h), and sucralfate[p] (43mg/kg PO q 8 h) throughout the entire duration of hospitalization. Although a colloid osmotic pressure was not measured, hydroxyethyl starch was continued due to the concern for decreased oncotic pressure based on persistent hypoalbuminemia (range 16.0–8.0 g/L [1.6–1.8 g/dL, RI, 25.0–37.0 g/L [2.5–3.7 g/dL]). Activated charcoal[q] (360 mg/kg PO q 6 h) and cholestyramine[r] (62.5 mg/kg PO q 6 h) were administered in a staggered fashion for 48 hours after extracorporeal therapy and then discontinued.

Approximately 18 hours after admission, the dog developed marked hematochezia and bleeding from his dialysis catheter site. Melena was unable to be detected due to the use of activated charcoal producing black stools. Fecal occult blood screening was not performed. A coagulation profile was performed, which revealed prolonged clotting times (prothrombin time 16.6 s, RI, 6.8–10.2 s; activated partial thromboplastin time 77.5 s, RI, 10.7–16.4 s), increased D-dimers concentration (0.30 μg/mL, RI, <0.2 μg/mL), and thrombocytopenia (25×10^9/L [25×10^3/μL], RI, 177–398 $\times$ 10^9/L [177–398 $\times$ 10^3/μL). The dog was treated with 240 mL of fresh frozen plasma (10.4 mL/kg) over 3 hours with no adverse reactions noted. The blood oozing at the catheter site and hematochezia significantly improved over the following days; however, a follow-up coagulation profile was not repeated.

The dog was discharged without renal or hepatic injury. An abbreviated biochemistry panel on the date of discharge revealed an ALT (59 U/L; RI, 16–91 U/L), creatinine (114.9 μmol/L [1.3 mg/dL]; RI, 61.9–59.1 μmol/L [0.7-1.8 mg/dL]), and BUN (3.9 mmol/L [11 mg/dL]; RI, 1.8–10.7 mmol/L [5–30 mg/dL]), all within the normal

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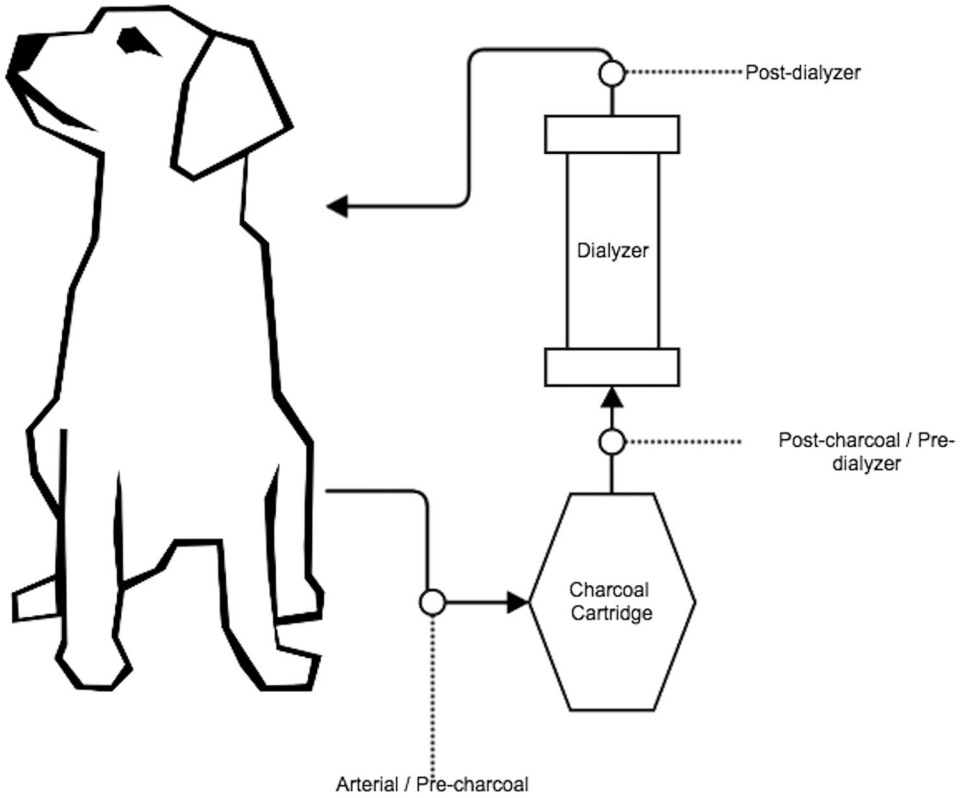

Figure 1: Schematic of extracorporeal circuit demonstrating blood sampling points.

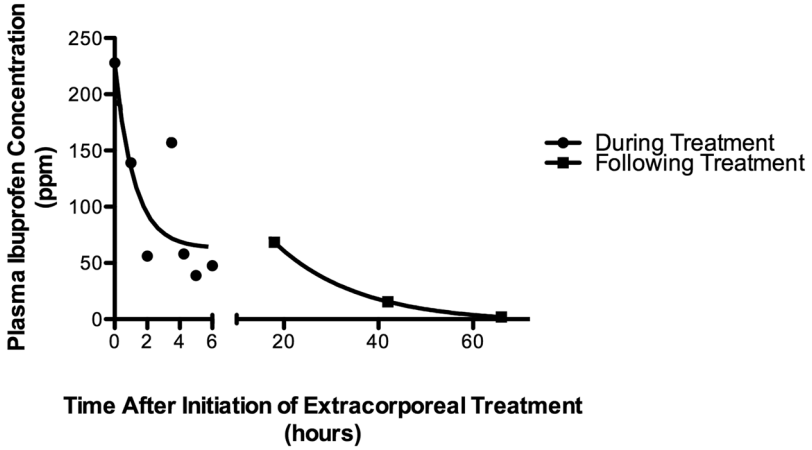

Figure 2: Serum ibuprofen concentration (ppm) measured during charcoal hemoperfusion therapy (solid line), immediately following treatment (broken circles) and throughout hospitalization (broken line).

RI. The dog was discharged home with gastrointestinal supportive medications, misoprostol (4.3 μg/kg PO q 6 h), ondansetron (0.66 mg/kg PO q 12 h), metronidazole (10 mg/kg PO q 12 h), sucralfate (43 mg/kg PO q 8 h), and omeprazole[s] (0.8 mg/kg PO q 24 h). Recheck abbreviated biochemical panel, complete blood count, and urinalysis performed one week following hospital discharge did not reveal any evidence of acute kidney injury or renal dysfunction, acute hepatopathy, or other complications.

Discussion

Ibuprofen is a commonly used nonsteroidal anti-inflammatory in people; however, it is not advocated for use in dogs. Ibuprofen ingestion is associated with

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Table 1: Serum ibuprofen concentration (ppm) measured prior to, during, and after charcoal hemoperfusion therapy

Time (hours post start of treatment)	Arterial-side serum ibuprofen concentration (ppm)	Postcharcoal (predialyzer) serum ibuprofen concentration (ppm)	Postdialyzer serum ibuprofen concentration (ppm)
0	228		
1	139	149	147
2	56.2	106	161
3.5	157	108	70.8
4.25	58	55.8	51
5	38.9	44.8	68.3
6	47.6	43.6	39.1
18	68.5		
42	15.6		
66	1.9		

Time points between hours 1 and 6 were taken during the treatment.

a number of adverse effects in the dog, including gastrointestinal upset, acute hepatopathy, acute kidney injury, and central nervous system alterations.[1–6] Many of these adverse effects are attributed to cyclooxygenase inhibition; however, the mechanism of action leading to neurologic abnormalities, such as seizure and coma, remains unknown.[1,2]

Before the availability of veterinary approved nonsteroidal anti-inflammatories, one recommended dosage of ibuprofen was 5 mg/kg/day orally in dogs. Due to the side effects, even at the recommended dose, it is generally not recommended for use in dogs.[4] Accidental toxicities in dogs are very common due to the popularity of this drug for human use. The severity of clinical signs is dose dependent with doses ≥25–125 mg/kg causing vomiting, diarrhea, melena, nausea, and abdominal pain; doses ≥175–200 mg/kg leading to acute kidney injury; and doses ≥400–500 mg/kg leading to central nervous system effects such as seizures, depression, and coma.[1,3] Exposure to doses >600 mg/kg is considered lethal in dogs.[1–3]

The pharmacokinetics of ibuprofen in dogs following oral administration of 5 mg/kg has previously been reported.[4] This study determined that the maximum serum concentrations were found between 0.5 and 3 hours post oral administration, the half-life was 4.6 hours, and it is 96% protein bound.[4] Following accidental ingestion, adverse clinical signs were absent when dogs had serum ibuprofen concentrations ≤31 μg/mL; melena and increased serum urea concentration were present when ibuprofen concentration was 138 μg/mL.[5] The half-life and rate of elimination are unknown in cases of accidental ibuprofen overdose; however, dogs with serum ibuprofen concentrations >130 μg/mL may take 48 hours to fall to <10 μg/mL.[5] Charcoal hemoperfusion in this patient reduced the serum concentration of ibuprofen by 79% over the 6-hour treatment, producing much more rapid elimination than endogenous clearance, although the exact pharmacokinetics of ibuprofen at such a high dose is unknown.

Treatment of ibuprofen toxicity involves gastrointestinal decontamination, oral activated charcoal and cholestyramine therapy, gastrointestinal protection, and intravenous fluid therapy. Cholestyramine is a nondigestible resin that binds to bile in the gastrointestinal tract to prevent enterohepatic recirculation of bile acids and associated bound substances, such as toxins, which are then excreted in the feces.[7] For patients with severe toxicity and CNS effects, therapy may also include anticonvulsant medications, repeated doses of naloxone, and respiratory support.[2] Recently, the use of intravenous lipid solution was documented to successfully treat severe ibuprofen toxicity in a dog.[8]

Given the severity of clinical signs in the dog, combination charcoal hemoperfusion and hemodialysis was performed immediately following the attempted gastric lavage. Hemodialysis alone likely would not have been sufficient to decrease serum ibuprofen concentrations, as in people ibuprofen and its metabolites are poorly removed by hemodialysis (mean extraction efficiency of 16.7%).[9] This is likely due to the extensive protein binding property of ibuprofen; protein-bound substances do not readily diffuse across the surface membrane of a traditional dialyzer. The small molecular size of ibuprofen suggests the unbound drug could easily be removed with hemodialysis; however, the extensive protein-binding (96%) precludes this from being effective alone in treating toxicity. Using a high-efficiency dialyzer would not significantly increase total drug elimination, as it would not increase the removal of the protein-bound ibuprofen. Percentage extraction across the dialyzer during this patient's treatment was actually an 8% increase, confirming the minimal clearance of ibuprofen via a conventional hemodialyzer

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alone. There was significant variation seen when comparing the predialyzer and postdialyzer samples. At some time points, the plasma ibuprofen was reduced as much as 34% across the dialyzer, and other times increased by 52%. This observation is difficult to explain, but could be due to adsorbed ibuprofen intermittently leaching from the hemodialyzer fibers, or potential variability within the accuracy of high-performance liquid chromatography. The removal of ibuprofen during hemodialysis has been previously reported to total <4% of the ingested dose, with a reported minimal effect on the elimination half-life.[9,10.] A charcoal cartridge added to the hemodialysis circuit allows for the removal of substances that are highly protein-bound, lipid-soluble, and have a high molecular weight, affording significant drug elimination. Despite the minimal extraction efficacy of the dialyzer, it was still used in combination with the charcoal hemoperfusion to maintain normoglycemia. The charcoal cartridge binds glucose and the dialysate fluid contains glucose to prevent hypoglycemia. In addition, the extracorporeal blood would not be warmed without the warmed dialysate, which could cause hypothermia if not used. Our data demonstrate saturation of the charcoal cartridge after 2 hours of hemoperfusion.

In the present patient, serum ibuprofen concentrations were measured via high-performance liquid chromatography. Initial serum concentration prior to extracorporeal treatment was 228 ppm. Approximately 3 hours into treatment, the patient roused from his comatose state, was extubated, and appeared only mildly disoriented. The serum ibuprofen concentration at that time was 157 ppm, further decreasing to 47.6 at the completion of the treatment, which was a 79% reduction. The patient was administered supportive medications including intravenous fluids, oral activated charcoal, and oral cholestyramine for the next 48 hours. Twelve hours beyond the end of the extracorporeal treatment, the patient's serum ibuprofen concentration was 68.5 ppm and decreased to 1.9 ppm over the following 48 hours, following first-order elimination.

Bleeding developed within 18 hours of hospitalization, which was likely due to the combination of marked thrombocytopenia, prolonged clotting times, and platelet function inhibition. The thrombocytopenia was likely due to loss of platelets as they adhered to the activated charcoal adsorbent during hemoperfusion, destruction of platelets by the surface irregularities of the charcoal cartridge, and from blood loss both from the suspected gastric ulceration and from the dialysis catheter site. Studies in people report thrombocytopenia as a common complication of hemoperfusion therapy with a decrease of up to 20–50% in the patient's platelet count following therapy.[11–13] The prolonged clotting times were likely due to the binding of the clotting factors in the charcoal cartridge. It is reported in the human literature that the use of charcoal cartridges leads to a decrease in coagulation factors (mainly II, V, IX, and X) by up to 10–25%.[11–13]

The use of mannitol for renoprotection remains controversial as its free radical scavenging effects have been mostly demonstrated in experimental models of kidney injury. The role of mannitol in preventing or treating acute kidney injury is not clearly defined. Despite this, mannitol remains a commonly used drug in the management and prevention of kidney injury.

The duration of hemoperfusion therapy needed for adequate ibuprofen serum clearance has not been reported in veterinary literature. In human medicine, a 4- to 6-hour treatment is usually sufficient to reverse side effects and to reduce serum concentrations of most toxins; however, ibuprofen is not explicitly listed.[13] Saturation of the charcoal cartridge occurs after 2–6 hours of use and this will result in a progressive reduction in the clearance of the toxin.[13] In the present case, the cartridge was changed at 3 hours to allow for greater clearance of ibuprofen.

This is the first report to highlight the use of a 6-hour treatment of charcoal hemoperfusion coupled serially with a conventional dialyzer to efficiently remove ibuprofen in cases of severe toxicity with minimal complications. This therapy is a unique and effective method to treat life-threatening toxicity of ibuprofen and many other substances. Referral to a hospital with hemoperfusion capabilities should be considered in patients with such toxicities.

Footnotes

[a] Advil, Pfizer, New York City, NY.
[b] Phox Ultra Stat Profile, Nova Biomedical Corporation, Waltham, MA.
[c] PlasmaLyte A, Abbott Laboratories, Chicago, IL.
[d] Schon XL, AngioDynamics, Inc, Latham, NY.
[e] Pheonix Hemodialysis System, Gambro, Lakewood, CO.
[f] Low-weight, low-volume cartridge blood set, Gambro.
[g] Adsorba 150 charcoal cartridge, Gambro.
[h] Fresenius F3 hemodialyzer, Fresenius Medical Care, Waltham, MA.
[i] Hydroxyethyl starch, Teva Parenteral Medicine, Inc, Irvine, CA.
[j] Hospira, Inc, Lake Forest, IL.
[k] Pennsylvania Animal Diagnostic Laboratory System, New Bolton Center, Kennett Square, PA.
[l] Greenstone LLC, Peapack, NJ.
[m] Esomeprazole sodium, AstraZeneca, Wilmington, DE.
[n] Ondansetron injectable, West-Ward Pharmaceutical Corp, Eatontown, NJ.
[o] Watson Pharmaceuticals, Inc, Parsippany, NJ.
[p] Sucralfate 1 gram, Sanofi-Aventis, Kansas City, MO.
[q] Nich UAA gel, Nih Marketing, Inc, Gulf Breeze, FL.
[r] Upsher-Smith Laboratories, Minnapolis, MN.
[s] Prilosec, AtraZeneca.

References

1. Villar D, Buck WB, Gonzalez JM. Ibuprofen, aspirin and acetaminophen toxicosis and treatment in dogs and cats. Vet Hum Toxicol 1998; 40(3):156–162.

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2. Khan SA, McLean M. Toxicology of frequently encountered nonsteroidal anti-inflammatory drugs in dogs and cats. Vet Clin Small Anim 2012; 42:289–306.
3. Dunayer E. Ibuprofen toxicosis in dogs, cats, and ferrets. Vet Med 2004; July:580–585.
4. Scherkl R, Frey HH. Pharmacokinetics of ibuprofen in the dog. J Vet Pharmacol Ther 1987; 10(3):261–265.
5. Jackson TW, Costin C, Link K, et al. Correlation of serum ibuprofen concentration with clinical signs of toxicity in three canine exposures. Vet Hum Toxicol 1991;33(5):486–488.
6. Jones RD, Baynes RE, Nimitz CT. Nonsteroidal anti-inflammatory drug toxicosis in dogs and cats: 240 cases (1989-1990). J Am Vet Med Assoc 1992; 201(3):475–477.
7. Scaldaferri F, Pizzoferrato M, Ponziani FR, et al. Use and indications of cholestyramine and bile acid sequestrants. Intern Emerg Med 2013; 8:205–210.
8. Bolfer L, McMichael M, Ngwenyama TR, et al. Treatment of ibuprofen toxicosis in a dog with IV lipid emulsion. J Am Anim Hosp Assoc 2014; 50(2):136–140.
9. Senekjian HO, Lee CS, Kuo TH, et al. Absorption and disposition of ibuprofen in hemodialyzed uremic patients. Eur J Rheumatol Inflamm 1983; 6(2):155–162.
10. Antal EJ, Wright CE, Brown BL, et al. The influence of hemodialysis on the pharmacokinetics of ibuprofen and its major metabolites. J Clin Pharmacol 1986; 26(3):184–190.
11. Winchester JF, MacKay JM, Forbes CD, et al. Hemostatic changes induced in vitro by hemoperfusion over activated charcoal. Artif Organs 1978; 2(3):293–300.
12. Sangster B, Heijst ANP, Sixma JJ. The influence of haemoperfusion on haemostasis and cellular constituents of blood in the treatment of intoxications. Arch Toxicol 1981; 47:269–278.
13. Ghannoum M, Bouchard J, Nolin TD, et al. Hemoperfusion for the treatment of poisonining: technology, derminants of poison clearance, and application in clinical practice. Semin Dial 2014; 27:350–361

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