



Management of Acetaminophen and Ibuprofen Toxicoses in Dogs and Cats

Jill A. Richardson, DVM
ASPCA Animal Poison Control Center
Urbana, IL

SUMMARY

Acetaminophen and ibuprofen are commonly used in humans for their analgesic, anti-pyretic, and anti-inflammatory (ibuprofen) effects. Between January 1998 and March 2000, veterinarians at the ASPCA National Animal Poison Control Center (NAPCC) consulted on more than 1,050 cases of accidental exposures to acetaminophen and 1,100 cases of ibuprofen ingestion in dogs and cats. Exposures to these medications can have serious effects on the animal's health. Fortunately, with prompt, aggressive treatment and good supportive care, most animals will recover completely.

ACETAMINOPHEN

Acetaminophen (4'-Hydroxyacetanilide N-acetyl-p-aminophenol N-(4-Hydroxyphenyl) acetamide) is a synthetic non-opiate derivative of p-aminophenol. Acetaminophen tablets, liquid preparations, and long acting compounds are available in over 200 prescription and non-prescription formulations and are also found in combination products.¹ Acetaminophen possesses analgesic and antipyretic activity similar to aspirin.^{1,2} Unlike aspirin, acetaminophen does not possess anti-inflammatory activity or platelet function effects.² Acetaminophen increases the pain threshold by inhibiting central cyclooxygenase and may inhibit chemical mediators that sensitize the pain receptors.^{1,3} Acetaminophen also inhibits the effects of pyrogen by blocking prostaglandin synthesis.² Acetaminophen toxicity can result from a single toxic dose or repeated cumulative dosages which lead to methemoglobinemia and hepatotoxicity.² In dogs, acetaminophen is used therapeutically for analgesia at a dose of 10 mg/kg BID.^{4,5} Clinical signs of toxicity are not typically observed in dogs unless the dose exceeds 100mg/kg, at which dose hepatotoxicity is possible. At 200mg/kg, methemoglobinemia is a possibility.⁵ There is no safe acetaminophen dose for cats.⁵ In cats, 10 mg/kg has produced signs of toxicity.⁶ Cats have less ability to metabolize acetaminophen because they are deficient in glucuronyl transferase.⁴

Toxicologic Mechanism

Acetaminophen is primarily eliminated through conjugation to inactive glucuronide and sulfate metabolites.^{1,2} Acetaminophen also undergoes minor metabolism by the P-450 mixed function oxidase to a highly reactive metabolite, N-acetyl-para-benzoquinoneimine (NAPQI), that is inactivated through glucuronidation with glutathione, in the liver.^{1,2,3,7} When glucuronidation and sulfation pathways become saturated and glutathione stores are depleted to less than 70% of normal values, NAPQI metabolite binds to the hepatic cell membrane and damages the lipid layer, causing hepatocyte injury and death.^{3,7} NAPQI also causes severe oxidative stress to red blood cells. The oxidant damage to heme ions results in methemoglobin. Ferrous iron is oxidized to ferric iron converting hemoglobin to methemoglobin, which does not carry oxygen.^{4,8} Oxidation of hemoglobin may also cause Heinz body formation.⁴

Clinical Signs

Clinical signs of acetaminophen toxicity are related to methemoglobinemia and hepatotoxicity. Clinical signs include depression, weakness, tachypnea, dyspnea, cyanosis, icterus, vomiting, methemoglobinemia, hypothermia, facial or paw edema, hepatic necrosis, and death.⁴ Methemoglobinemia causes the mucous membranes to appear muddy or brown in color and is usually accompanied by tachycardia, tachypnea, weakness, and lethargy.⁸ Centrilobular necrosis is the most common form of hepatocellular damage seen with acetaminophen toxicity.^{1,9} Liver necrosis is considered to be less common with cats than with dogs.¹⁰ Large doses of acetaminophen can also cause nephrotoxicity characterized by proximal tubule necrosis.¹¹

Diagnosis

The diagnosis of acetaminophen toxicity is most often based upon exposure history and the development of associated clinical signs. Qualitative acetaminophen plasma levels can be obtained through human hospitals to confirm exposure (4 hours post exposure levels are recommended).¹ Other toxicological rule outs for methemoglobinemia include naphthalene, local anesthetics, other oxidant drugs (pyridium,

phenazopyridine), nitrite, and chlorates. Other common hepatotoxic substances include iron, some mycotoxins, phosphorus, carbon tetrachloride, coal tar, phenolics, nitrosamines, thiacetarsamide, some benzimidazole anthelmintics, tannic acid, copper, vitamin A, pyrrolizidine alkaloid containing plants, blue green algae, and Amanita mushrooms.

Treatment

The objective of treatment in acetaminophen toxicity is to replenish glutathione, convert methemoglobin back to hemoglobin, and prevent or treat hepatic necrosis. Stabilization is always a priority. If the animal is dyspneic, oxygen therapy should be given. Whole blood transfusions or Oxyglobin® may be necessary. Although the prognosis is good if animal is treated promptly and aggressively, animals with severe signs of methemoglobinemia or hepatic damage have poor to guarded prognosis.

Decontamination:

Emesis should be induced in asymptomatic dogs or cats, unless contraindications exist.^{12,13} Gastric lavage is considered to be less effective than emesis but may be performed if emesis is contraindicated.¹³ Activated charcoal at a dose of 1-3 grams/kg adsorbs acetaminophen and should be repeated. A two to three hour wait between activated charcoal administration and oral administration of N-acetylcysteine (NAC) is recommended, since activated charcoal can adsorb NAC as well as acetaminophen. A cathartic should be used in combination with activated charcoal, unless the animal is dehydrated or has diarrhea. Forced diuresis or peritoneal dialysis does not enhance elimination of acetaminophen.²

Replenish glutathione

NAC directly binds with acetaminophen metabolites to enhance elimination and serves as a glutathione precursor.^{10,14} NAC can reduce the extent of liver injury or methemoglobinemia by providing an alternate substrate for conjugation with the reactive metabolites of acetaminophen and by maintaining or restoring glutathione levels.^{10,14,15} NAC is given orally to dogs or cats at an initial loading dose of 140 mg/kg and then 70 mg/kg every 4 hours for at least 3-5 treatments.^{10,14} For severely affected animals, an initial dose of 280 mg/kg PO or IV is recommended.¹³ NAC is not labeled for IV use, however, the loading dose can be given slowly IV, in life threatening cases, over a period of 15 to 20 minutes, with use of 0.2 micron bacteriostatic filter.¹³ Anaphylaxis has been reported with IV use of NAC, but administration of antihistamines is usually effective in countering the signs.⁷

Adjunctive therapy

Ascorbic acid (vitamin C) provides a reserve system for the reduction of methemoglobin back to hemoglobin.^{4,6} However, ascorbic acid has questionable efficacy and may cause GI upset.¹ The effective dose of Vitamin C is 30 mg/kg BID-QID oral or injectable. Cimetidine can inhibit the cytochrome p-450 oxidation system in the liver and may be useful in reducing the metabolism of acetaminophen, although its ability to preventing acetaminophen induced hepatotoxicity is controversial.^{1,6} The dose of cimetidine is 5-10 mg/kg PO, IM, or IV every 6-8 hours in dogs and cats.¹⁴ The use of cimetidine in combination with NAC and ascorbic acid has been shown to be more effective than any of the agents alone in preventing acetaminophen-induced hepatotoxicity in animal studies.⁶ The patient should be monitored for the presence of methemoglobinemia. In cats, methemoglobin values increase within 2-4 hours, followed by Heinz body formation.⁸ Methemoglobinemic blood appears chocolate brown in color. The liver enzymes should be monitored closely. Laboratory evidence of hepatotoxicity generally develops 24-36 hours post ingestion. Large doses of acetaminophen can cause nephrotoxicity with increases in BUN and creatinine levels and decreases in GFR.¹¹ The duration of treatment depends on the dosage of acetaminophen ingested and the clinical signs presented. Treatment for hepatic necrosis may continue for weeks.

IBUPROFEN

Ibuprofen (2-(p-Isobutylphenyl) propionic acid) is a substituted phenylalkanoic acid with nonsteroidal anti-inflammatory, antipyretic, and analgesic properties.² Ibuprofen is available in 50,100, 200, 300, 400, 600, and 800 mg tablets and pediatric suspensions in 40 mg/mL and 100 mg/5 ml strengths.^{1,2} Ibuprofen can also be found as a 5% ibuprofen topical ointment and in combination with decongestants in cold or flu medications.¹ Ibuprofen is used as an anti-inflammatory in the treatment of arthritis, as an analgesic in the treatment of acute and chronic musculoskeletal pain, and as an antipyretic. Ibuprofen inhibits prostaglandin synthesis by blocking the conversion of arachidonic acid to prostaglandins.^{4,12,16,17} Prostaglandins stimulate repair of gastrointestinal epithelial cells, stimulate secretion of bicarbonate by epithelial cells, and stimulate water and electrolyte movement into small intestine. ^{4,12,16,17} Ibuprofen has been used therapeutically in dogs at 5 mg/kg, but because it can cause gastric ulcers and perforations, it is generally not recommended.^{4,18} According to studies of acute ingestion of ibuprofen in dogs, vomiting, diarrhea, nausea, anorexia, gastric ulceration, and abdominal pain can be seen with doses of 50-125mg/kg; these signs in combination with

renal damage can be seen at levels at or above 175 mg/kg; and at levels at or above 400 mg/kg, CNS effects such as seizure, ataxia, coma, ataxia may occur.⁷ Cats are considered to be twice as sensitive as dogs because they have a limited glucuronyl-conjugating capacity.^{7,17,19} Ibuprofen decreases secretion of the protective mucous layer in stomach and small intestine and can cause vasoconstriction in gastric mucosa, all of which may contribute to ulcer formation.^{4,12,16,17} Ibuprofen can also inhibit significantly decrease renal blood flow, glomerular filtration rate, tubular ion transport, renin release, and water homeostasis.^{1,2} Ibuprofen may also affect platelet aggregation and possibly hepatic function.² Serious hepatotoxicosis does not appear to be a common problem with ibuprofen.^{12,16}

Clinical Signs

Most common signs of ibuprofen toxicoses include anorexia, nausea, vomiting, lethargy, diarrhea, melena, ataxia, polyuria, and polydipsia.^{1,2,12} In addition weakness, hypotension, and seizures can be seen. Cardiac arrhythmias such as hypotension, bradycardia, tachycardia, and atrial fibrillation have been reported in human overdose of ibuprofen. Acute renal failure, severe CNS depression, hyperkalemia, respiratory depression, and metabolic acidosis are also possible, although serious acid-base disturbances are rare and usually transient.^{1,2,12} Post-mortem lesions associated with ibuprofen toxicoses include perforations, erosion, ulceration, and hemorrhage of the upper (stomach and duodenum) and, on occasion, lower (colon) gastrointestinal tract.¹⁶ In humans, the onset of gastrointestinal upset is generally within the first 2-6 hours after ingestion, with the onset of gastrointestinal hemorrhage and ulceration occurring 12 hours to 4 days post ingestion. The onset of renal failure, in humans, often occurs within the first 12 hours after massive exposure to NSAID, but may be delayed up to 3-5 days post exposure.² In a review of 35 cases of ibuprofen ingestion in dogs, 7 vomited shortly after exposure and 6 developed vomiting or hematemesis within 20 to 24 hours after exposure.² Severe hemorrhagic gastroenteritis developed 48 hours after exposure in one case.²

Diagnosis

The diagnosis of ibuprofen toxicity in dogs or cats is usually based upon exposure history and the development of associated clinical signs. Ibuprofen blood levels are not widely available, although qualitative analysis could be performed on serum, urine, or hepatic tissues using gas chromatography and mass spectrophotometry.^{2,18} Other toxicological rule outs for renal failure include ethylene glycol, lily toxicosis in the cat, calcipotriene, cholecalciferol, and zinc toxicity.

Treatment

The primary goal of treatment is to prevent or treat gastric ulceration, renal failure, CNS effects, and possibly hepatic effects. Prognosis is good if animal is treated promptly and appropriately. Delay in treatment can decrease survival potential with large exposures.

Stabilization

Assisted ventilation and supplemental oxygen may be required if the animal is comatose. Seizures should be treated with diazepam (0.5-1.0 mg/kg IV in increments of 5-10 mg to effect in cats and dogs).^{12,14,19} Intravenous fluids, whole blood, inotropic agents such as dopamine (2-5 micrograms/ kg per minute in dogs and cats), and electrolytes should be given to control hypotension and hemorrhage, manage acute bleeding ulcers, maintain renal function, and correct electrolyte abnormalities.^{14,19} Acid base imbalances should be corrected. Metabolic acidosis is treated with slow IV infusion of sodium bicarbonate in fluids. Bicarbonate and fluid therapy must be monitored closely via blood gases and adjusted if pulmonary edema or metabolic alkalosis develops.

Decontamination:

Decontamination procedures with ibuprofen are similar to those described for acetaminophen toxicoses. Activated charcoal adsorbs ibuprofen and should be repeated, since ibuprofen undergoes enterohepatic recirculation. Forced diuresis, dialysis or hemoperfusion does not enhance ibuprofen elimination.^{12,16}

Prevention of Renal Failure

Fluid diuresis for 24-48 hours is recommended with ibuprofen doses approaching or exceeding 175 mg/kg in dogs or 87 mg/kg in cats.) The use of dobutamine (5-20 microgram/kg/min IV infusion in dogs) may increase renal perfusion.¹⁴ Peritoneal dialysis may be necessary if unresponsive oliguric or anuric renal failure develops. The development of papillary necrosis is most likely an irreversible condition.^{12,17}

Gastric Protection

Gastric protection is an important part of treating an ibuprofen toxicosis. Gastric protection is recommended for at least 5-7 days. Misoprostol (Cytotec®) may be helpful for treating or preventing gastric ulceration caused by ibuprofen.^{4,14,20} Misoprostol is a synthetic prostaglandin that inhibits gastric acid and has a cytoprotective effect on gastric mucosa.^{14,20} Misoprostol also stimulates mucus and bicarbonate secretion and increases gastric mucosal blood flow. The dosage used in dogs is 1-3 mcg/kg q6-8 hours PO.^{14,20} Sucralfate can be used to bind to erosions and ulcers and protect them from exposure to gastric acid, bile acids, and or pepsin.¹⁴ Sucralfate may also be cytoprotective by stimulating prostaglandin production.¹⁴ Sucralfate is given at 0.5 to 1 gram every 8-12 hours PO in dogs and 0.25 gram every 8-12 hours in cats.¹⁴ Since sucralfate may bind to other drugs and delay absorption, it is recommended to wait 2 hours before administering other medications.^{12,20}

Other helpful medications

H2 antagonists inhibit histamine and decrease gastric acid secretion and may be helpful with ibuprofen overdoses. Ranitidine is 3-13 times more potent as cimetidine and can be given at 2 mg/kg every 8 hours IV or PO in dogs and 2.5 mg/kg every 12 hours IV or 3.5 mg/kg every 12 hours PO in cats.^{14,20} The use of cimetidine with ibuprofen toxicosis appears to be controversial. Cimetidine decreases hepatic blood flow and inhibits hepatic microsomal enzymes.^{14,21} Pretreatment with cimetidine was found to increase both the rate and extent of absorption of ibuprofen in rats.²¹ However, the extent of cimetidine-mediated decrease in clearance with single-dose ibuprofen ingestion in humans is considered insignificant.²² Metoclopramide (0.2 to 0.4 mg/kg every 6-8 hours PO or SC in dogs and cats) can be used to control vomiting.^{4,14,20} Mild gastrointestinal irritation may be treated symptomatically with antacids, such as magnesium or aluminum hydroxide. Bismuth subsalicylate antacid formulations are contraindicated.^{4,12,20}

Ancillary treatment

When renal failure is a potential, BUN, creatinine, and urine specific gravity should be monitored closely. A baseline level and then rechecks at 36, 48, and 72 hours is recommended. The animal should also be monitored for acidosis and electrolyte shifts during treatment. Symptomatic treatment for gastric signs and renal failure should be given until the animal fully recovers.

REFERENCES

1. AHFS Drug Information. Acetaminophen. American Society of Health-System Pharmacists. Edited by McEvoy, GK; 1815, 1937, 2000.
2. Poisindex® CD-ROM, Acetaminophen and Ibuprofen. Toxicological Management Denver: Microdex Inc. Expires 9-2000.
3. Insel, PA: Analgesic, Antipyretic and Antiinflammatory Agents and Drugs Employed in Treatment of Gout. The Pharmacological Basis of Therapeutics, 9th Edition. McGraw-Hill, New York; 617-655, 1996.
4. Perry, H: Acetaminophen. Clinical Management of Poisoning and Overdoses. Clinical Management of Poisoning and Drug Overdose, 3rd ed. W.B. Saunders Company, Philadelphia; 88-198,1998
5. Fisher, DJ: Disorders of Red Blood Cells. Handbook of Small Animal Practice, 3rd Edition. Saunders, Philadelphia; 656-673, 1997.
6. Osweiler, Gary. Household Drugs. The Handbook of Small Animal Practice, 3rd Edition, Churchill Livingstone, New York: 1279-1283; 1997.
7. Villar D & Buck WB: Ibuprofen, aspirin, and acetaminophen toxicosis and treatment in dogs and cats. Vet Human Toxicol; 40:156-162, 1998.
8. Aaronson, LR: Acetaminophen Toxicosis in 17 Cats. Journal of Veterinary Emergency and Critical Care. Vol6., No2; 65-69, 2000.
9. Haschek, Wanda M. Hepatobiliary System. Fundamentals of Toxicologic Pathology. Academic Press, San Diego; 127-151, 1998.
10. Oehme FW Aspirin and Acetaminophen: Kirk RW Current Veterinary Therapy IX. Philadelphia: WB Saunders; 188-190, 1986.
11. Goldstein,RS, Schnellmann, RG: Toxic Responses of the Kidney. Toxicology, The Basic Science of Poisons. McGraw-Hill, New York. 417-442; 1996.
12. Kore, Anita M. Toxicology of Nonsteroidal Anti-inflammatory Drugs. Veterinary Clinics of North America: Small Animal Practice. Volume 20, No. 2; 419-428,1998
13. Beasley, VR, et al: A Systems Affected Approach to Veterinary Toxicology. University of Illinois Press, Urbana, Illinois;27-69, 862-864, 1999.
14. Plumb, DC: Veterinary Drug Handbook, 3rd ed. Iowa State University Press, Ames Iowa; 8,134, 462, 562, 583,434, 221; 1999.
15. Donova, J Ward. Nonsteroidal Antiinflammatory Drugs and Cochicine. Clinical Management of Poisoning and Drug Overdose, 3rd edition. 687-699;1998.
16. Rumbelha, Wilson K. Nephrotoxins , Veterinary Therapy XIII Small Animal Practice. 212-217;2000.

17. Owens-Clark, Jane, Dorman, David C. Toxicity from Newer Over the Counter Drugs. *Veterinary Therapy XIII Small Animal Practice*. 227-231;2000.
18. Cathers, TE: Acute Ibuprofen Toxicosis in a Ferret. *JAVMA*, Vol. 216, No.9. 1426-1428; 2000.
19. Willard, M. D. Gastrointestinal Drugs. *Clinical Pharmacology and Therapeutics*. Volume 28, Number 2. 2000; 377-392;1998.
20. Parrott KA, Christensen JM: Influence of cimetidine on the disposition of ibuprofen in the rat. *Res Commun Chem Pathol Pharmacol*. Mar;43(3):369-80; 1984.
21. Ochs HR, et al: Interaction of ibuprofen with the H-2 receptor antagonists ranitidine and cimetidine. *Clin Pharmacol Ther*. Dec;38(6):648-51;1985. ASPCA Animal Poison Control Center. Unpublished data. Urbana, Illinois. 1995-1997.

Copyright © 2000, *The Journal of Veterinary Emergency and Critical Care*. Reprinted with permission from the July-September 2000 issue. All rights reserved. For more on *JVECC*, visit <http://www.veccs.org/>.