

# Management of Acetaminophen and Ibuprofen Toxicoses in Dogs and Cats

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

*Address reprint requests to:*

Jill A. Richardson, DVM  
ASPCA Animal Poison Control Center  
1717 Philo Road, Suite #36  
Urbana, IL 61802

## *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 Animal Poison Control Center (APCC) 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. (*Vet Emerg Crit Care, 10:285-291, 2000*)

## **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.<sup>(1)</sup> Acetaminophen possesses analgesic and antipyretic activity similar to aspirin.<sup>(1,2)</sup> Unlike aspirin, acetaminophen does not possess anti-inflammatory activity or platelet function effects.<sup>(2)</sup> Acetaminophen increases the pain threshold by inhibiting central cyclooxygenase and may inhibit chemical mediators that sensitize the pain receptors.<sup>(1,3)</sup> Acetaminophen also inhibits the effects of pyrogens by blocking prostaglandin synthesis.<sup>(2)</sup>

Acetaminophen toxicity can result from a single toxic dose or repeated cumulative dosages

which lead to methemoglobinemia and hepatotoxicity.<sup>(2)</sup> In dogs, acetaminophen is used therapeutically for analgesia at a dose of 10 mg/kg q 12 h.<sup>(4,5)</sup> Clinical signs of toxicity are not typically observed in dogs unless the dose exceeds 100 mg/kg, at which dose hepatotoxicity is possible. At 200 mg/kg, methemoglobinemia is a possibility.<sup>(5)</sup> There is no safe acetaminophen dose for cats.<sup>(5)</sup> In cats, 10 mg/kg has produced signs of toxicity.<sup>(6)</sup> Cats have less ability to metabolize acetaminophen because they are deficient in glucuronyl transferase.<sup>(4)</sup>

## *Toxicologic Mechanism*

Acetaminophen is primarily eliminated through conjugation to inactive glucuronide and sulfate metabolites.<sup>(1,2)</sup> 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.<sup>(1,2,3,7)</sup> 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.<sup>(3,7)</sup> 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.<sup>(4,8)</sup> Oxidation of hemoglobin may also cause Heinz body formation.<sup>(4)</sup>

### *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.<sup>(4)</sup>

Methemoglobinemia causes the mucous membranes to appear muddy or brown in color and is usually accompanied by tachycardia, tachypnea, weakness, and lethargy.<sup>(8)</sup> Centrilobular necrosis is the most common form of hepatocellular damage seen with acetaminophen toxicity.<sup>(1,9)</sup> Liver necrosis is considered to be less common in cats than in dogs.<sup>(10)</sup> Large doses of acetaminophen could also cause nephrotoxicity characterized by proximal tubule necrosis, although the exact level is unknown in dogs and cats.<sup>(11)</sup>

### *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).<sup>(1)</sup> The differential diagnosis must consider other toxicological causes of

methemoglobinemia and possible exposure to other common hepatotoxic substances. The list of toxic agents to consider is shown in tables 1 and 2.

### *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. Packed red cell transfusions or polymerized hemoglobin solutions (Oxyglobin®) may be necessary for treatment of anemia or to increase oxygen-carrying capacity. Although the prognosis is good if the animal is treated promptly and aggressively, animals with severe signs of methemoglobinemia or hepatic damage have poor to guarded prognoses.

**Decontamination:** Emesis should be induced in asymptomatic dogs or cats, unless contraindications exist.<sup>(12,13)</sup> Gastric lavage is considered to be less effective than emesis, but may be performed if emesis is contraindicated.<sup>(13)</sup> Activated charcoal at a dose of 1-3 grams/kg adsorbs acetaminophen and should be repeated, since acetaminophen undergoes enterohepatic recirculation. A two to three hour delay 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.<sup>(2)</sup>

**Replenish glutathione:** NAC directly binds with acetaminophen metabolites to make them inactive and serves as a glutathione precursor.<sup>(10,14)</sup> 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.<sup>(10,14,15)</sup> A 5% solution of NAC is given orally

to dogs or cats at an initial loading dose of 140 mg/kg and then 70 mg/kg every q 4 h for at least 3-5 treatments. <sup>(10,14)</sup> For severely affected animals, an initial dose of 280 mg/kg PO or IV is recommended. <sup>(13)</sup> NAC is not labeled for IV use, however, the loading dose can be given IV slowly in life-threatening cases, over a period of 15 to

20 minutes with use of 0.2 micron filter. <sup>(13)</sup> Anaphylaxis has been reported with IV use of NAC, but administration of antihistamines is usually effective in countering the signs. <sup>(7)</sup>

**Adjunctive therapy:** Ascorbic acid (vitamin C) provides a reserve system for the reduction of methemoglobin back to hemoglobin. <sup>(4,6)</sup>

## Toxicological Rule-outs

**TABLE 1:**

### HEPATOTOXIC AGENTS

Acetaminophen	Iron	Cycad species
Amanita mushrooms	Aspirin	Aflatoxins

**TABLE 2:**

### AGENTS ASSOCIATED WITH METHEMOGLOBINEMIA

Naphthalene	Local Anesthetics	Chlorates
Phenazopyridine	Pyridium	Nitrite

**TABLE 3:**

### NEPHROTOXIC AGENTS

Ibuprofen and other NSAIDS	Ethylene Glycol	Calcipotriene
Zinc	Cholecalciferol	Certain Lilies in Cats

However, ascorbic acid has questionable efficacy and may cause GI upset.<sup>(1)</sup> The effective dose of vitamin C is 30 mg/kg q 6-12 h orally or intravenously.

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 prevent acetaminophen-induced hepatotoxicity is controversial.<sup>(1,6)</sup> The dose of cimetidine is 5-10 mg/kg PO, IM, or IV every q 6-8 h in dogs and cats.<sup>(14)</sup> 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.<sup>(6)</sup>

**Ancillary treatment:** The patient should be monitored for the presence of methemoglobinemia. In cats, methemoglobin values increase within 2-4 hours, followed by Heinz body formation.<sup>(8)</sup> 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 (exact level is unknown in dogs or cats) of acetaminophen can cause nephrotoxicity with increases in BUN and creatinine levels, and decreases in glomerular filtration rate (GFR).<sup>(11)</sup>

The duration of treatment depends on the dosage of acetaminophen ingested and the clinical signs presented. Extensive and prolonged treatment for hepatic necrosis may be required.

## ***IBUPROFEN***

Ibuprofen (2-(p-Isobutylphenyl) propionic acid) is a substituted phenylalkanoic acid with nonsteroidal anti-inflammatory, antipyretic, and analgesic properties.<sup>(2)</sup> 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.<sup>(1,2)</sup> Ibuprofen can also be found as a 5% ibuprofen topical ointment and in combination with decongestants in cold or flu medications.<sup>(1)</sup> 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.<sup>(4,12,16,17)</sup> Prostaglandins stimulate repair of gastrointestinal epithelial cells, stimulate secretion of bicarbonate by epithelial cells, and stimulate water and electrolyte movement into small intestine.<sup>(4,12,16,17)</sup>

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.<sup>(4,18)</sup> 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 50-125 mg/kg; these signs in combination with renal damage can be seen at doses at or above 175 mg/kg; and at doses at or above 400 mg/kg CNS effects such as seizure, ataxia, and coma, may occur.<sup>(7)</sup> Cats are considered to be twice as sensitive as dogs because they have a limited glucuronyl-conjugating capacity.<sup>(7,17,19)</sup>

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.<sup>(4,12,16,17)</sup> Ibuprofen can also significantly decrease renal blood flow, glomerular filtration rate, tubular ion transport, renin release, and water homeostasis.<sup>(1,2)</sup> Ibuprofen may also affect platelet aggregation and possibly hepatic function.<sup>(2)</sup> Serious hepatotoxicosis does not appear to be a common problem with ibuprofen.<sup>(12,16)</sup>

## ***Clinical Signs***

Most common signs of ibuprofen toxicoses include anorexia, nausea, vomiting, lethargy, diarrhea, melena, ataxia, polyuria, and polydipsia.<sup>(1,2,12)</sup> In addition, weakness, hypotension, and seizures can be seen. Cardiac arrhythmias such as hypotension, bradycardia, tachycardia, and atrial fibrillation have been reported in human overdoses of ibuprofen.<sup>(1)</sup> 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.<sup>(1,2,12)</sup>

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.<sup>(16)</sup>

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.<sup>(2)</sup> 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.<sup>(2)</sup> Severe hemorrhagic gastroenteritis developed 48 hours after exposure in one case.<sup>(2)</sup>

### *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 concentrations are not widely available, although qualitative analysis could be performed on serum, urine, or hepatic tissues using gas chromatography and mass spectrophotometry.<sup>(2,18)</sup> If signs of renal failure are also present, a differential diagnosis of other causes of nephrotoxicity should be considered (table 3).

### *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 the 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.<sup>(12,14,19)</sup>

Intravenous fluids should be given to control hypotension, maintain renal function, and correct electrolyte abnormalities.<sup>(14,19)</sup> Blood products may be required for treatment of anemia and hypovolemia secondary to acute bleeding ulcers. Acid base imbalances should be corrected. Severe 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.<sup>(12,16)</sup>

**Prevention of Renal Failure:** Fluid diuresis for 24-48 hours is recommended when ibuprofen doses approach or exceed 175 mg/kg in dogs or 87 mg/kg in cats. The use of dopamine (3-5 microgram/kg/min IV infusion) in dogs may increase renal perfusion.<sup>(14)</sup> Peritoneal dialysis may be necessary if unresponsive oliguric or anuric renal failure develops. The development of papillary necrosis is most likely an irreversible condition.<sup>(12,17)</sup>

**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.<sup>(4,14,20)</sup> Misoprostol is a synthetic prostaglandin (PGE<sub>1</sub>) that inhibits gastric acid and has a cytoprotective effect on gastric mucosa.<sup>(14,20)</sup> Misoprostol also stimulates mucus and bicarbonate secretion and increases gastric mucosal blood flow. The dosage used in dogs is 1-3 mg/kg q 6-8 hours PO.<sup>(14,20)</sup> Sucralfate can be used to bind to erosions and ulcers, and protect them from exposure to gastric acid, bile acids, and pepsin.<sup>(14)</sup> Sucralfate may also be cytoprotective by stimulating prostaglandin (PGE<sub>2</sub> and PGI<sub>2</sub>) production.<sup>(14)</sup> Sucralfate is

given at 0.5 - 1 gram q 8-12 h PO in dogs, and 0.25 gram every 8-12 h in cats.<sup>(14)</sup> Since sucralfate may bind to other drugs and delay absorption, it is recommended to wait 2 hours before administering other medications.<sup>(12,20)</sup>

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

**Ancillary treatment:** When renal failure is a potential, BUN, creatinine, and urine specific gravity should be monitored closely. A baseline level with 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 provided until the animal fully recovers.

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