

# ACETAMINOPHEN AND CATS

## A Dangerous Combination

Vera Steenbergen, CVT  
ASPCA Animal Poison Control Center  
Urbana, Illinois

No dose of acetaminophen  
is safe for cats.



Your clinic receives a call from a frantic owner who had placed two acetaminophen tablets on her nightstand and went to get a glass of water. When she returned, the pills were missing. Callie, her 12-year-old domestic shorthair cat, was sitting next to the nightstand. This occurred several hours ago. Now Callie is lethargic and vomiting, and her breathing appears somewhat labored. The owner suspects that the cat swallowed the pills. You ask the owner to bring Callie in immediately because of the high likelihood of life-threatening acetaminophen ingestion.

Acetaminophen is available in over 200 prescription and nonprescription formulations.<sup>1,2</sup> Strengths range from 80-mg tablets in children's formulations to 500-mg extra-strength tablets. Over-the-counter products are formulated as plain acetaminophen and in combination with other compounds, such as aspirin, caffeine, and decongestants. Prescription products may contain opioids, such as hydrocodone. Acetaminophen is used in humans for treating pain and fever. Although published therapeutic doses of acetaminophen are available for dogs and cats, the drug is not commonly used in these species because of its low level of safety.<sup>3</sup>

### KINETICS

Acetaminophen is a synthetic nonopiate derivative of *p*-aminophenol and a member of the coal tar family of analgesics. It is absorbed rapidly and almost completely from the gastrointestinal tract. The drug is poorly protein bound and widely distributed throughout the body.<sup>2,4</sup> It is metabolized primarily in the liver, but some of it is metabolized in the kidneys as well. Metabolites are primarily excreted through the bile.

Acetaminophen is primarily eliminated by two major pathways: glucuronidation and sulfation. When these pathways are saturated or deficient, an alternative pathway breaks down the acetaminophen to a toxic metabolite called *NAPQI*<sup>a</sup> – a free radical that damages hemoglobin, red blood cells (RBCs), and, occasionally, kidney cells. Cats are deficient in glucuronidation and sulfation abilities and, therefore, more susceptible to acetaminophen toxicosis than dogs. Cats have been shown to produce signs of acetaminophen toxicosis at a dose as low as 10 mg/kg.<sup>2,5</sup>

*NAPQI* can bind to the hepatic cell membrane and damage the lipid layer, causing hepatocyte injury and death.<sup>2,6,7</sup> It also causes severe oxida-

tive stress to RBCs.<sup>4</sup> The oxidant damage to heme molecules results in methemoglobin. Oxidation of hemoglobin may also cause Heinz body formation. Damaged RBCs may be subsequently removed from circulation, causing anemia.

### TOXICITY

Acetaminophen toxicosis may result from a single exposure, which leads to methemoglobinemia and/or hepatotoxicity in cats. Large doses of acetaminophen can also cause nephrotoxicity, with increases in blood urea nitrogen and creatinine levels and decreases in glomerular filtration rate.<sup>2,8</sup>

Because of the structure of their hemoglobin, cats are much more sensitive to RBC injury than are dogs. In a report on two cats with acetaminophen toxicosis, one cat survived with treatment.<sup>9</sup> The other cat died and was shown to have cardiomyopathy, which may have made this cat more susceptible to acetaminophen toxicity. Perhaps the safest way to look at acetaminophen toxicity in cats is that no dose is safe.

### CLINICAL SIGNS

Signs of acetaminophen toxicosis in cats may occur within a few hours of ingestion. The most common signs in cats are **depression, weakness,**

<sup>a</sup>*N*-acetyl-para-benzequinoneimine.

tachypnea, dyspnea, cyanosis, vomiting, methemoglobinemia, facial and/or paw edema, and death.<sup>2,9,10</sup>

Hematuria and hemoglobinuria may appear first, when blood methemoglobin levels are around 20%. Methemoglobinemia causes the mucous membranes to appear muddy or brown and is usually accompanied by tachycardia, tachypnea, weakness, and lethargy. Dyspnea may be seen as methemoglobin levels reach or exceed 35%.

## DIAGNOSIS

The diagnosis of acetaminophen toxicity is most often made by the exposure history and development of associated clinical signs. A rapid bench-top test that may be helpful entails placing a drop of the patient's blood next to a drop of normal blood on white filter paper. Blood containing excess methemoglobin appears chocolate brown in contrast to normal blood.

Diagnostic differentials for methemoglobinemia include toxicoses associated with propylene glycol, nitrates, phenazopyridine, naphthalene, and local anesthetics (e.g., benzocaine).

## TREATMENT

When a cat with acetaminophen toxicosis arrives at the clinic, stabilization is the priority. Oxygen should be administered if the cat is dyspneic. Giving whole blood transfusions or Oxyglobin (Biopure) may be necessary. Both have been used to improve oxygen-carrying capacity of blood in severe cases. Oxyglobin has been successfully used (extralabel) to treat severely dyspneic cats with acetaminophen toxicosis.<sup>2</sup>

If the patient is asymptomatic, emesis should be induced unless otherwise contraindicated by underlying conditions.<sup>2,11,12</sup> Although less effective, gastric lavage may be necessary if emesis is contraindicated or unsuccessful.<sup>2,12</sup> Activated charcoal should be administered and repeated because acetaminophen undergoes enterohepatic recirculation. After giving activated charcoal, a cathartic should be administered if the cat is not experiencing life-threat-

### Glossary

**Glucuronidation** — Metabolic pathway in which glucuronide is combined with an agent to enhance excretion of the agent

**Heinz body formation** — Change in the usual nature of hemoglobin in RBCs as a result of oxidative injury

**Heme molecules** — Iron-containing protein molecules that form the oxygen-carrying component of hemoglobin

**Sulfation** — Metabolic pathway in which sulfate is combined with an agent to enhance the excretion of the agent

ening signs.<sup>2,13</sup> Many forms of activated charcoal contain a cathartic, such as sorbitol, and when repeated doses of activated charcoal are administered, the cathartic should be given with every third charcoal dose.

The development of methemoglobinemia or hepatic injury may be minimized by administering *N*-acetylcysteine (NAC). NAC is used to bind with NAPQI, which enhances elimination and minimizes cell injury. It also serves as a glutathione precursor. NAC may be administered at a loading dose of 140 to 280 mg/kg PO or IV q4h for at least three to five treatments.<sup>2,12</sup> The NAC is diluted in D5W to a 5% solution before administration.<sup>2,3,14</sup> Because of the extended half-life of acetaminophen in cats, NAC should be given to cats with clinical signs regardless of time since ingestion.

An alternative treatment is the combination of cimetidine with NAC and ascorbic acid. This combination has been shown to be more effective than any one agent alone in minimizing acetaminophen-induced hepatotoxicity.<sup>2,5</sup> Ascorbic acid (vitamin C) may aid in converting methemoglobin to oxyhemoglobin. The recommended dose of vitamin C is 30 mg/kg q6–12h PO or IV.<sup>1,2,5</sup> Cimetidine, an H<sub>2</sub>-receptor antagonist, is an inhibitor of cytochrome P-450 oxidase in the liver and may help reduce the metabolism of acetaminophen to NAPQI.<sup>2,3</sup> The dose of cimetidine is 5 to 10 mg/kg PO, IM, or IV q6–8h. Use this cautiously in geriatric patients or patients with impaired hepatic or renal function.

An agent being used with some suc-

cess for hepatic injury due to acetaminophen is *S*-adenosylmethionine. It may also be helpful in the long-term management of hepatic injury due to acetaminophen. The dose is 18 mg/kg for 1 to 3 months.

Another alternative treatment is methylene blue. A solution of 10% methylene blue in sterile saline (100 mg/1 ml saline) is prepared and given IV at a dose of 1.5 mg/kg. This agent may be effective in reversing methemoglobinemia but is very risky to use in cats because methylene blue can actually induce methemoglobin formation.<sup>13</sup>

(Corticosteroids and antihistamines are generally contraindicated in cases of acetaminophen toxicity. Also, physical activity should be limited and stress avoided in dyspneic cats.<sup>13</sup>)

The length of treatment depends on the dose ingested and the clinical signs the animal is showing. Hepatic damage could require weeks of treatment. The prognosis depends on how quickly the cat receives treatment, the severity of clinical signs, and the dose ingested. Cats with severe signs of methemoglobinemia or with hepatic damage have a poor to guarded prognosis.

## DIET

One final note is that research has shown a higher incidence of acetaminophen-induced methemoglobinemia in cats fed a diet high in propylene glycol than in those fed diets low in propylene glycol. Wet cat food contains 7% to 13% propylene glycol, which may induce methemoglobinemia or Heinz body formation in cats. The

preexistence of RBC injury due to propylene glycol consumption may contribute to increased sensitivity of RBCs to oxidative stress caused by acetaminophen ingestion.<sup>13</sup>

*Callie was very lucky. After being treated with NAC and oxygen (for dyspnea), she was released from the hospital several days later without hepatic or renal damage. Although acetaminophen exposure in cats can be fatal, successful outcomes are possible with prompt and aggressive veterinary care.*

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**Cushing's Disease** (continued from p. 41)

**Glossary**

**Adrenal gland** — Located at the front end of the kidneys, it has two components: The cortex produces steroid hormones, and the medulla produces epinephrine and norepinephrine

**Corticotropin (adrenocorticotropic hormone; ACTH)** — A hormone secreted by the pituitary gland that stimulates the adrenal gland to secrete more cortisol

**Cortisol** — A naturally occurring steroid produced by the adrenal cortex; it serves many purposes, including regulating the immune system and the metabolism of glucose, protein, and fats

**Creatinine** — A nitrogenous compound; an elevation in the creatinine level in the blood indicates a disturbance in kidney function

**Dexamethasone** — A synthetic glucocorticoid used as a screening test for Cushing's disease

**Iatrogenic** — Caused by influences outside the body

**Pituitary gland** — Located at the base of the brain, it secretes ACTH and stimulates the adrenal gland

**Polydipsia** — Excessive thirst resulting in excessive water intake

**Polyphagia** — Increased appetite

**Polyuria** — Excessive urination

Cushing's disease should be one of the primary rule-outs. However, many dogs with the disease do not have these signs, especially early on. If you notice recent weight gain and a potbellied appearance or thinning or an absence of the haircoat in a symmetrical pattern on the back, flanks, or sides in a dog that presents for any reason, you should mention these signs to the veterinarian.

Because doses of dexamethasone and ACTH are very small and easily miscalculated, careful calculation is critical. Double-check your calculations before administration. Also be sure to draw the sequential serum samples at the recommended time (usually dictated by your reference laboratory).

The client handout on page 42 can make this complicated disease easier for clients to understand. VI