Acetaminophen is a common household pain reliever and fever reducer frequently used by humans. Most people do not realize that while this drug may be relatively safe for them, it can be very toxic to their pets. The American Society for the Prevention of Cruelty to Animals Poison Control Center reports that of the 1,464 calls regarding acetaminophen ingestion by both dogs (1,232) and cats (232) received between 1992 and 1997, 95% involved deliberate administration of the drug by the owner. Although accidental ingestion is more commonly seen in dogs, cat intoxication most often results from owner administration for some nondescript malady (pain, lethargy, fever). Toxicity in dogs commonly causes liver damage, while methemoglobinemia is the primary manifestation in cats. However, methemoglobinemia, although rare, can be seen in dogs and liver damage can be seen in cats, usually in association with higher doses or in animals with preexisting conditions.

The toxic dose of acetaminophen is 100 to 200 mg/kg in dogs and as low as 10 mg/kg in cats. This means that just one regular-strength Tylenol (325 mg) can be toxic in a 4-kg cat. This discrepancy is mainly related to differences in the hepatic metabolism of the drug. Three competing pathways in the liver are responsible for acetaminophen breakdown. Two of these pathways, glucuronidation and sulfation, produce nontoxic metabolites that are excreted in bile and urine. The third pathway involves oxidation by cytochrome P450 and results in the formation of the reactive intermediate N-acetyl-para-benzoquinoneimine (NAPQI); this compound is responsible for the toxic effects seen with acetaminophen ingestion. In cats, the main pathway for metabolism is through conjugation with a sulfate compound. This route is easily saturated. Glucuronidation is limited in cats because of reduced activity of the UDP-glucuronosyltransferase enzyme. These factors lead to a decreased ability to eliminate the drug and an increased shunting through the cytochrome P450 pathway with subsequent toxic metabolite formation. Even though dogs are more resistant to acetaminophen toxicity, it is important to remember that even one extra-strength tablet (500 mg acetaminophen) could be toxic to a very small dog, reaching the lower end of the toxic dose range.

NAPQI will conjugate with reduced glutathione to produce a nontoxic product that is excreted in the urine. This reaction can protect the patient from the damaging effects of NAPQI at low doses. However, glutathione stores quickly become depleted with continued exposure, leading to an accumulation of NAPQI. NAPQI is then free to react with proteins in the liver, resulting in hepatocellular damage, and it is also free to cause oxidative damage to erythrocytes. Feline hemoglobin is more susceptible to oxidative stress than is canine hemoglobin. This is because of the presence of eight reactive sulfa hydroxy groups per hemoglobin molecule versus four in the canine. Methemoglobin is formed from the oxidation of iron in hemoglobin from the ferrous to the ferric state. This compromises the oxygen-carrying capacity of blood as methemoglobin is unable to transport oxygen. The oxyhemoglobin curve is shifted to the left, decreasing oxygen release at the tissue level. Resultant clinical signs associated with this tissue hypoxia include respiratory distress, cyanosis, tachycardia, and mentation changes and are usually seen once the level of methemoglobin has reached approximately 20% or greater of the hemoglobin concentration. As erythrocytes are further damaged, hemoglobin denatures and precipitates to form Heinz bodies, an irreversible reaction. This increases the fragility of the erythrocytes, leading to hemolysis and anemia. Onset of anemia can be delayed 24 to 48 hours because of slow hemolysis, so monitoring hematocrit is essential in this time frame.

**DIAGNOSTIC CRITERIA**

**Historical Information**

**Gender, Age, and Breed Predispositions:** None.

**Owner Observations:** Owners may notice signs of intoxication, including lethargy, brown mucous membranes, and respiratory distress, as soon as 1 hour after ingestion. Some cats will also experience edema of the face and forelimb paws.
Other Historical Considerations: Owners frequently administer acetaminophen to their cats to help alleviate some nonspecific ailment, such as lethargy or inappetance, not knowing its toxic effects. Also, tablets set aside by the owner may “disappear.”

Physical Examination Findings
- Brown mucous membranes.
- Cyanosis.
- Respiratory distress or tachypnea.
- Tachycardia.
- Lethargy, depression, or coma.
- Edema of the face and paws.
- Hypothermia.
- Weakness or collapse.
- Icterus.
- Nausea, vomiting, and/or anorexia.

Laboratory Findings
Complete blood count, chemistry panel, urinalysis, and blood gas analysis should be conducted. Abnormal findings include:
- Methemoglobinemia, recognized by dark brown–colored blood.
- Increased serum alanine aminotransferase (normal range, 26–77 IU/L) and aspartate aminotransferase (normal range, 14–41 IU/L); abnormalities can range from mild to severe depending on the degree of hepatic damage.
- Heinz body anemia.
- Increased total serum bilirubin (normal range, 0.1–0.2 mg/dl).
- Qualitative acetaminophen assays can be performed by a human laboratory; elevated level indicates intoxication.

Other Diagnostic Findings
Histopathology of liver biopsy sample (or necropsy):
- Unlike the situation in dogs, hepatic necrosis is uncommon in cats but can occur.
- Hepatic degenerative changes (pericholangitis, mononuclear cell infiltrates, and vacuolated hepatocytes) can be seen.
- Biliary stasis and bile duct proliferation can also be seen, although uncommonly.

Summary of Diagnostic Criteria
- History of owner administration.
- Methemoglobinemia with brown mucous membranes.

CHECKPOINTS
- Oxyglobin (Biopure) transfusion has been suggested to aid in oxygen delivery as well as to provide colloidal support in shocky patients. The benefits of its use are still under debate and remain to be scientifically proven. In cats, a dose of 20 ml/kg should not be exceeded because some cats have developed volume overload pulmonary edema at doses of 30 ml/kg and higher. $–$$
- Cimetidine (Tagamet, GlaxoSmithKline) has been shown to inhibit the cytochrome P450 oxidation pathway and subsequently may help decrease the formation of NAPQI. It is believed to be most efficacious if given at a dosage of 5–10 mg/kg IV or IM q6h for 48 hours shortly after intoxication. Effectiveness of this therapy has yet to be clinically proven, and there has yet to be a consensus as to its value as a treatment. $

- Respiratory distress.
- Edema of face and paws.

Diagnostic Differentials
Facial Swelling
- Allergic reaction or anaphylaxis: Often pruritic; absence of methemoglobinemia.
- Lymphatic obstruction (neoplasia, abscess, granuloma): Palpable mass; absence of methemoglobinemia.

Oxidative Damage to Erythrocytes; Anemia
- Other causes of oxidative damage to erythrocytes, including onion or garlic intoxication, methimazole, benzocaine, or propylthiouracil. A thorough history can often reveal administration of or access to these compounds.
- Immune-mediated hemolytic anemia: Spherocytes and/or autoagglutination evident on blood smear; blood is discolored red, not brown.
- Zinc toxicity: Metallic gastrointestinal foreign bodies seen on radiographs.

Respiratory Distress or Cyanosis
- Cardiomyopathy: Auscultation often reveals a gallop rhythm and/or a murmur. Thoracic radiography and echocardiography reveal evidence of heart disease.
- Pulmonary disease (feline asthma, pneumonia, pulmonary edema, parasites): Thoracic radiography often reveals parenchymal changes.
ON THE NEWS FRONT
Antioxidants such as S-adenosylmethionine (SAMe) are being investigated to determine their efficacy in limiting the oxidative damage to erythrocytes. Results thus far are promising, and their use may become more of a mainstay in the treatment of acetaminophen toxicity in the future.

TREATMENT RECOMMENDATIONS

Initial Treatment
Provide Supportive Care
- Minimizing stress is essential.
- Oxygen support is often considered beneficial.
- Intravenous fluid therapy should be instituted to provide hemodynamic support and treat for shock.
- Packed erythrocytes or whole blood transfusion may be required in cats with severe anemia (packed cell volume [PCV] less than 15%; see below).

Decrease Absorption
Acetaminophen is rapidly absorbed from the gastrointestinal tract. Therefore, attempts to limit systemic absorption are generally useful only if made within the first 2 hours after ingestion. The following procedures can be very stressful to the patient, and their potential benefit must be weighed against the risk of stress and aspiration:
- Vomiting can be induced (xylazine [Rompun, Bayer Animal Health], 0.44–1.1 mg/kg IM or SC once) if the patient is sufficiently alert. In addition, gastric lavage may be beneficial. Apomorphine (0.03 mg/kg IV or 0.3 mg/kg in the subconjunctival sac as a single dose; alternatively, a tablet can be placed in the subconjunctival sac and rinsed out after emesis has been induced) or hydrogen peroxide (3% solution at 1–2 ml/kg PO) could be used for emesis; these agents have fewer side effects than xylazine but may be less effective.
- Activated charcoal (1–3 g/kg PO q8h for 24 hours) can be administered. A cathartic should be used with the first dose unless contraindicated. However, activated charcoal may adsorb N-acetylcysteine (NAC), reducing its effect. Since it is not recommended to delay treatment with NAC, activated charcoal should be withheld for at least 2 hours after NAC administration.

Administer Glutathione Precursor
NAC (Mucomyst, various manufacturers) provides a source of cysteine for glutathione synthesis. This increases antioxidant protection from the toxic effects of NAPQI and thus decreases methemoglobin formation. It also provides sulfate that can be utilized for conjugation, supporting metabolism of acetaminophen to a nontoxic compound. NAC may also have an antioxidant effect by directly reducing free radicals.
- Dose: 140 mg/kg PO or IV as a loading dose, then 70 mg/kg q6h for seven treatments. The oral route is believed to be superior because a higher concentration of drug is presented to the liver through the portal circulation. For severe cases, a dose of 280 mg/kg PO or IV is recommended as the initial dose in dogs.
- If given IV, the 10% or 20% solution should be diluted with 5% dextrose to make a 5% solution that is given through a 0.2 µm Millipore filter over 30 to 60 minutes. NAC can cause phlebitis and, if given too quickly, can also cause hypotenion or bronchospasm. Some believe pretreatment with diphenhydramine helps to decrease possible anaphylactic reactions to NAC.

Reverse Damage
Ascorbic acid (vitamin C; 30 mg/kg IV q6h until a resolution of methemoglobinemia is noted) is proposed to act as an antioxidant to reduce methemoglobin to hemoglobin. Its efficacy in doing so is questionable; however, adverse side effects are absent, so potential benefit outweighs any risk.

Alternative/Optional Treatments/Therapy
- Oxyglobin (5–15 ml/kg IV) may be useful in the treatment of cats with methemoglobinemia. However, this use is off-label and still considered somewhat controversial. (See Checkpoints for further discussion.) $–$$
- S-adenosylmethionine (SAMe; see On the News Front, above).
- Blood transfusions may be needed in the treatment of anemia due to Heinz body formation and hemolysis. A good rule is that 1 ml/lb will raise the PCV by 1% if whole blood is used and 1 ml/kg will raise PCV by 1% if packed cells are used. A common dose is 20 ml/kg. $–$$
- If hepatic failure is present, coagulopathies may be
Evidence of improvement includes decreasing respiratory distress, normalization of mucous membrane color, resolving facial and paw edema, improved mentation, and resolution of laboratory abnormalities.

In cats, acetaminophen half-life varies based on the amount ingested. At 20 mg/kg, half-life is only 0.6 hours, but increase the dose to 60 mg/kg and half-life increases to 2.4 hours.

Supportive Treatment $-$ $$$
- Sodium bicarbonate can be given to treat severe metabolic acidosis (blood pH less than 7.1 that does not respond to appropriate fluid therapy), although this is an uncommon clinical problem.
- If the cat is eating, kitten food should be fed because of its higher concentration of sulfhydryl group substrates.
- The importance of continued supportive care, including minimal stress and adequate hydration, nutrition, and nursing care, cannot be emphasized enough.

Patient Monitoring
- Respiratory rate and effort should be monitored for an increase in respiratory distress.
- Mental status should be closely evaluated for deterioration.
- PCV should be checked for evidence of Heinz body anemia.
- Mucous membrane color should return to normal with resolution of methemoglobinemia following treatment.
- Treatments are administered every 6 hours for 48 hours.

Home Management
- Administration of acetaminophen to cats is contraindicated under any circumstance.
- Sources of potential accidental ingestion should be removed.

Milestones/Recovery Time Frames
- If death occurs, it usually happens within the first 18 to 36 hours.

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