

Acetaminophen Toxicity



DEFINITION/OVERVIEW

- Acetaminophen (N-acetyl-p-aminophenol) is a common OTC or prescription medication with antipyretic and analgesic properties. It is commonly known as “Tylenol,” APAP, or paracetamol.
- Acetaminophen does not have antiinflammatory properties and is not considered an NSAID.
- Acetaminophen can result in accidental toxicosis in dogs, cats, and ferrets. Ingestion may be accidental or by well-intentioned pet owners who are unaware of the toxic dose or safety profile of this common medication.
- In dogs, clinical signs of toxicosis are seen at >100–150 mg/kg, while in cats and ferrets, toxic doses can be seen at 10–50 mg/kg.
- Acetaminophen toxicosis results in methemoglobinemia (cats, less commonly dogs) or hepatotoxicity (dogs, less commonly cats).
- Clinical signs of toxicosis typically include malaise, anorexia, paw or facial swelling, vomiting, respiratory distress, brown mucous membranes, and icterus.
- Unlike the majority of toxicants, acetaminophen toxicosis *does* have an antidote N-acetylcysteine (NAC), making the prognosis fair to excellent with supportive care.



ETIOLOGY/PATHOPHYSIOLOGY

- Acetaminophen is a COX-3 inhibitor.
- Acetaminophen is metabolized through two pathways: the major pathway creates inactive metabolites through conjugation to inactive glucuronide and sulfate metabolites. The other pathway metabolizes acetaminophen by the cytochrome p450 enzyme pathway to the toxic metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Toxicosis occurs when the metabolic pathways for glucuronidation and sulfation are depleted; this results in toxic metabolites building up and secondary oxidative injury to RBCs and hepatic proteins.
- Acetaminophen is rapidly absorbed from the stomach and GIT; peak blood levels are reached within 30–60 minutes.

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Companion website: www.fiveminutevet.com/emergency

Systems Affected

- Gastrointestinal: vague GI signs may be seen early in acetaminophen toxicosis; more severe signs may be seen with advanced hepatic failure.
- Skin/exocrine: facial or paw swelling may be seen in both cats and dogs via an unknown mechanism; icterus with hepatotoxicity.
- Hemic/lymphatic/immune: oxidative injury to RBC and Hb molecules following glutathione depletion, resulting in MetHb and Heinz body anemia.
- Respiratory: respiratory distress secondary to the presence of MetHb and the inability to carry oxygen.
- Cardiovascular: shock secondary to anemic hypoxia.
- Hepatobiliary: hepatocellular injury and hepatic necrosis due to NAPQI.
- Nervous: hepatic encephalopathy secondary to hepatotoxicity.
- Ophthalmic: KCS has been reported with acetaminophen in dogs, even at subtoxic doses.
- Renal/urologic: rarely, large doses can result in renal tubular necrosis; this has only been reported in humans.



SIGNALMENT/HISTORY

Risk Factors

- Puppies and younger dogs appear to be overrepresented with poisoning due to their curious nature.
- Neonates, geriatric patients, or those with underlying hepatic disease may be more at risk for acetaminophen toxicosis due to abnormal or delayed metabolism.
- Cats are more susceptible to acetaminophen toxicosis, as they lack sufficient glucuronyl transferase to metabolize acetaminophen and have limited sulfate-binding capacity. Cats are also more susceptible as their hemoglobin contains eight sulfhydryl groups compared to four in other species; this makes feline RBC more prone to oxidative injury and results in MetHb developing earlier into toxicosis.
- Chronic administration.

Historical Findings

- Evidence of a tampered or chewed container or prescription bottle.
- Owner administration.
- Clinical signs consistent with acetaminophen toxicosis.



CLINICAL FEATURES

- Gastrointestinal.
 - Anorexia
 - Hypersalivation
 - Vomiting
 - Diarrhea

- Melena
- Abdominal pain
- Miscellaneous.
 - Facial or paw swelling
 - Generalized malaise
 - Hypothermia
- Hemic/lymphatic/immune.
 - Brown or cyanotic mucous membranes
 - Hemoglobinemia
 - Hemoglobinuria
- Respiratory.
 - Tachypnea progressing to dyspnea
 - Brown-colored mucous membranes
 - Increased respiratory rate and effort
- Cardiovascular.
 - Tachycardia
 - Hypotension
 - Cardiovascular collapse
- Hepatobiliary.
 - Malaise
 - Icterus
 - Bruising
 - Melena
- Nervous.
 - Dull mentation
 - Generalized malaise
 - Ataxia
 - Head pressing, star gazing, or abnormal mentation
 - Tremors
 - Seizures
 - Coma
- Ophthalmic.
 - Mucopurulent discharge
 - Squinting
 - Rubbing at the eyes
 - Conjunctivitis



DIFFERENTIAL DIAGNOSIS

- In patients presenting with increased liver enzymes or evidence suggestive of hepatopathy, other hepatotoxicants (e.g., sago palm, *Amanita* mushroom, xylitol, blue-green algae, aflatoxins, etc.), metabolic causes (e.g., cholangiohepatitis, extrahepatic biliary duct obstruction, pancreatitis, etc.), neoplasia, or infectious (e.g., *Leptospira*, etc.) causes should be ruled out.

- In patients presenting with anemia, other differential diagnoses include toxicants (such as zinc, mothballs (e.g., naphthalene), *Allium* spp. (e.g., onions, garlic, etc.), local anesthetics (e.g., benzocaine, etc.)), metabolic causes (e.g., IMHA), infectious causes (e.g., *Mycoplasma felis*, etc.), neoplasia, etc.



DIAGNOSTICS

- If an ingestion approaching a toxic dose has occurred, baseline blood work should include a CBC, biochemistry panel, and blood smear (to look for the presence of Heinz bodies) at the time of admission.
 - Common clinicopathologic findings seen with acetaminophen toxicosis include Heinz bodies, anemia, increased liver enzymes (typically seen 24–36 hours post ingestion), hyperbilirubinemia, hemoglobinemia, hemoglobinuria.
 - An extra drop of blood should be placed on a white paper towel to look for a dark or brown appearance; the presence of “dark” (deoxygenated) blood is suggestive of MetHb.
- Blood gas analysis:
 - May reveal the presence of a metabolic acidosis
 - In a patient with severe respiratory distress, an ABG can be performed to help rule out acetaminophen toxicosis; the presence of a normal PaO₂ with a low oxygen saturation is highly suspicious of toxicosis. Cooximetry can be used to measure MetHb, but is not readily available in veterinary medicine.
- Serum acetaminophen levels can be performed at a human hospital; levels are typically the most elevated 1–3 hours post ingestion. However, toxic levels in dogs and cats are not well established, and likely can only be used to confirm ingestion.
- In hospitalized patients, a daily PCV/TS and hepatic panel should be performed every 24 hours. If liver enzymes are normal after 48 hours and the patient is no longer symptomatic, the patient can be discharged after this time.
- In patients suspected of having hepatic injury (e.g., increased liver enzymes, hypoglycemic, hypocholesterolemia, etc.), a PT/PTT should be performed.
- Abdominal ultrasound + liver aspirate may be necessary in some cases to rule out other differential diagnoses.



THERAPEUTICS

- The mainstay therapy for acetaminophen toxicosis is administration of activated charcoal, oxygen therapy, intravenous (IV) fluid therapy, antidotal therapy (e.g., NAC), and hepatoprotectants (e.g., SAME).
- Decontamination.
 - Due to the rapid absorption of acetaminophen from the stomach and GIT, emesis induction is *not* recommended. Rather, immediate administration of one dose of activated charcoal (1–5 g/kg, PO) with a cathartic (e.g., sorbitol) is warranted provided the patient is asymptomatic.

- As acetaminophen undergoes some enterohepatic recirculation, multiple doses of activated charcoal (with the additional doses being free of a cathartic) should ideally be administered, provided the patient is asymptomatic and parenteral administration of NAC is available. If NAC is only available orally, only one dose of charcoal should be administered, with antidotal therapy prioritized after 2 hours of administration of charcoal.
- Oxygen therapy.
 - In tachypneic or patients with severe respiratory distress, immediate oxygen therapy is warranted to help treat anemic hypoxemia.
- Fluid therapy.
 - The use of a balanced, isotonic crystalloid is warranted to help hydrate and perfuse the patient.
- Antidotal therapy.
 - The use of NAC is warranted to help act as a glutathione source and to limit formation of the toxic metabolite NAPQI. This should be implemented as soon as possible.
- Blood products.
 - In cats with severe respiratory signs, transfusion of PRBC or whole blood may be warranted, even with a normal PCV. As MetHb is unable to carry oxygen appropriately, treatment should be aimed at antidotal therapy and oxygen support; if, however, the patient fails to respond clinically, administration of blood products may be necessary to deliver hemoglobin to treat anemic hypoxia.
 - In severe cases of acute hepatic failure secondary to acetaminophen, administration of FP or FFP (10–20 mL/kg, IV) may be necessary to provide vitamin K₁-dependent coagulation factors II, VII, IX, X.
- Hepatoprotectants.
 - The use of SAME is warranted to help reduce oxidative injury, and to act as a benign antioxidant and glutathione source.
- Miscellaneous.
 - Coagulopathic patients (secondary to liver failure) should be treated with vitamin K₁.
 - Vitamin C (ascorbic acid) can be used as a benign antioxidant, but in this author's experience does not appear to be clinically beneficial.
 - Methylene blue can be used to treat dogs with severe MetHb, and acts as an electron donor to reduce MetHb to Hb. This should not be used in cats, as it can cause Heinz body anemia.
- Gastric protectants.
 - The routine use of H₂ blockers, such as Cimetidine, is *no longer warranted or recommended* to prevent p450 enzyme interference with acetaminophen metabolism.

Drugs of Choice

- N-acetylcysteine (NAC): 140–280 mg/kg IV or PO loading dose, followed by 70 mg/kg IV or PO q6 hours × 48 hours or until clinical signs resolve.
- SAME: 18 mg/kg PO q24 hours × 14–30 days on an empty stomach.

- Antiemetics.
 - Maropitant (1 mg/kg SQ q24 hours; extralabel use in cats and via IV route); if evidence of hepatic failure is present, alternative antiemetics should be used.
 - Ondansetron: 0.1–0.5 mg/kg IV q12 hours.
 - Dolasetron: 0.6 mg/kg IV q24 hours.
- Vitamin K₁: 1 mg/kg PO or SQ q12–24 hours.
- Vitamin C: 30 mg/kg PO or SQ q6 hours.
- Methylene blue: 1.5 mg/kg IV 1–2×, slow (dogs only).
- KCS treatment.
 - Topical artificial tears OU, if indicated.
 - Topical cyclosporine ointment OU, if indicated.

Precautions/Interactions

- Acetaminophen is commonly combined with other ingredients such as opioids or opioid-like drugs (e.g., codeine, hydrocodone, oxycodone, propoxyphene, pentazocine, tramadol, etc.), decongestants (e.g., pseudoephedrine), antihistamines (e.g., chlorpheniramine, diphenhydramine), antitussives (e.g., dextromethorphan), NSAIDs (e.g., aspirin), and stimulants (e.g., caffeine). Dual toxicosis and variable clinical signs may occur as a result.

Alternative Drugs

- Ideally, a parenteral source of NAC should be used to allow additional GIT decontamination (with multiple doses of charcoal). While extralabel, the use of inhalational NAC (Mucomyst®) can be administered IV, using sterile technique and a 0.22 micron filter. Please see a drug reference book for appropriate dosing and dilution.



COMMENTS

Client Education/Prevention/Avoidance

- Owners should be educated to appropriately pet-proof the house. Education on crate training is imperative.
- Pet owners should be educated to never give an OTC or prescription medication to their pet without consulting their veterinarian first.
- Owners and veterinary professionals should be educated to call veterinary-specific poison control centers for consultation with a veterinary toxicologist for life-saving advice as needed.

Possible Complications

- In cases where acute hepatic injury has occurred, pet owners should be educated that chronic hepatopathy may develop.

- While acetaminophen (typically in combination with hydrocodone or oxycodone) can be used therapeutically in dogs as an alternative analgesic drug, therapeutic use in cats is *never* recommended. In dogs, even with therapeutic doses, potential adverse effects can be seen (e.g., KCS).

Expected Course and Prognosis

- Overall, the prognosis for acetaminophen toxicosis is fair to good, as the antidote NAC is readily available. However, financial limitations may preclude treatment, which often requires hospitalization for 24–72 hours.
- If clinical signs of acute hepatic failure or hepatic encephalopathy are present, the prognosis for survival is much poorer.

Synonyms

- Tylenol
- Paracetamol
- APAP
- Percoset
- Vicodin
- Any medication with the term “headache” listed
- Any medication with the term “cold and sinus” listed

Abbreviations

APAP:	N-acetyl-p-aminophenol
CBC:	complete blood count
COX:	cyclooxygenase
FFP:	fresh frozen plasma
FP:	frozen plasma
GI:	gastrointestinal
GIT:	gastrointestinal tract
Hb:	hemoglobin
IMHA:	immune-mediated hemolytic anemia
IV:	intravenous
MetHb:	methemoglobinemia
NAC:	N-acetylcysteine
NAPQI:	N-acetyl-para-benzoquinoneimine
NSAID:	nonsteroidal antiinflammatory drug
OTC:	over the counter
OU:	each eye (oculus uterque)
PCV:	packed cell volume
PO:	per os
PRBC:	packed red blood cells

PT: prothrombin time
PTT: partial thromboplastin time
SAmE: S-adenosyl-methionine
SQ: subcutaneous

Suggested Reading

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