NSAID Toxicity in Cats and Dogs

2 CE Hours

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Learning objectives

- List and explain some of the reasons that NSAIDs are considered more risky in cats and dogs than humans.
- List clinical signs of NSAID toxicosis associated with the gastrointestinal system.
- Explain how NSAIDs use can lead to stomach ulceration.
- Explain enterohepatic cycling, its significance in NSAID toxicity, and how to address it.
- Distinguish between syrup of ipecac and extract of ipecac.
- Discuss the pros and cons of gastric lavage in NSAID toxicity.

Introduction

According to the American Veterinary Medical Association (AVMA) over-the-counter drug poisoning is one of the most common poison exposures for small animals. This chapter will examine some of the most commonly consumed medications responsible for poisoning dogs and cats. Known as non-steroidal anti-inflammatory drugs (NSAIDS), the category includes aspirin, ibuprofen and acetaminophen.

Non-steroidal anti-inflammatory drugs (NSAIDs) appear in hundreds of prescription and non-prescription formulas and have a good track record for safety and effectiveness in humans. In some cases, they are administered to pets by pet-owners to relieve symptoms associated with arthritis or other painful conditions. Unfortunately, NSAIDs can be very dangerous when ingested by cats and dogs.

This chapter examines the clinical signs, action mechanisms and treatment of aspirin, ibuprofen and acetaminophen toxicity in dogs and cats. Because each pharmacological product is different, treatment should be tailored to the specific animal and the specific toxin.

NSAIDs

In some cases, animals consume large amounts of NSAIDs out of sight of their owners (plastic pill containers can be mistaken for chew toys or may come open when batted around by cats). Do your best to identify the drug and estimate how much has been ingested. Ask the pet owners to bring in the remainder of the bottle, if available, and any information regarding the medication. Try to find out exactly when ingestion occurred.

While some NSAIDs are prescribed for companion animals (to treat orthopedic conditions in dogs, for example), many are more likely to put the animal at risk. Because toxic effects result from chronic use (pet-owners administering it to ease pain in a pet), caution pet owners to check with the veterinarian before administering any medications on their own, as drugs are metabolized very differently and it is difficult to extrapolate dosage based on therapeutic doses in other species. Additionally, individual factors, such as the animal’s age, dehydration or cardiac disease, affect how the drug is metabolized. Decreased renal circulation slows excretion of the drug and risks potential renal damage. Hepatic or renal dysfunction also delays drug excretion.

Though NSAIDs share many characteristics, the degree of toxicity and action mechanisms vary between different compounds of the medication and affect different species in different ways. Cats, for example, are more susceptible to aspirin and acetaminophen toxicity than dogs, while dogs are very sensitive to ibuprofen.

Clinical signs

Gastrointestinal irritation is common, as are lethargy, anemia, melena and hematemesis. In cases of perforation, signs will include abdominal pain, shock, injected sclera, dark red mucous membranes, and tachycardia. Temperature may be low or high, and the pulse may be weak or bounding.

Pets with acute renal failure shows signs of hyposthenuria or isosthenuria, renal tubular cell casts in urine sediment, and/or glucosuria without hyperglycemia. Urine GGT (gamma-glutamyl transpeptidase) is elevated, with increased BUN (blood urea nitrogen) and creatinine, and electrolyte disturbances.

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Action mechanism

Cyclooxygenase is an unsaturated fatty acid responsible for converting arachidonic acid into prostaglandins, which are required for many normal body functions. Cyclooxygenase comes in two forms: cyclooxygenase 1 (COX 1) and cyclooxygenase 2 (COX 2).6 7 Cox 1 produces prostaglandins associated with bicarbonate secretion and the formation of protective gastric mucus. COX 2 is required for normal kidney function.

The suppression of gastric prostaglandins is the main mechanism responsible for the gastrointestinal toxicity of NSAIDs. When NSAIDs inhibit cyclooxygenase, it results in reduced production of prostaglandins, which results in reduced blood flow to the gastrointestinal tract, which reduces production of protective gastric mucus. There is also potential for gastrointestinal ischemia and ulceration, with potential for perforation. Because prostaglandins are also responsible for renal blood flow, NSAID poisoning can result in renal papillary necrosis and renal failure. Some of the more recently developed NSAIDS have fewer toxic side effects.

Due to significant differences in enterohepatic recycling, NSAIDs tend to be more toxic in cats and dogs than humans.8 In this cycle, bile salts and other substances excreted by the liver are absorbed by the intestinal mucosa and returned to the liver through the portal vein.

Treatment notes

There is no antidote for most NSAID toxicity. For exposure of less than two hours with no signs of toxicity, induce emesis and administer activated charcoal. Address gastrointestinal ulceration, perforation and acute renal failure as necessary.

EMERGENCY TREATMENT

Procedures

- Clear the airway and ventilate, if necessary.
- Administer supplementary oxygen.
- Treat shock or control seizures.
- Collect blood and urine for labwork: biochemical profile, electrolytes, venous or arterial blood gases and urinalysis.
- Insert urethral catheter and administer crystalloid. (noncolloid) solution to maintain urine output of at least 2-3 mL/kg/hr in dogs, and 1-2 mL/kg/hr in cats. Rapid onset of oliguria or anuria associated with NSAID overdose significantly increases the risk of overhydration. Monitor animal closely, including venous pressure, if possible.
- Monitor urine for evidence of perforation or renal damage. If perforation is suspected:
  - Confirm with abdominocentesis. If abdominocentesis does not confirm, consider diagnostic peritoneal lavage.
  - Perform exploratory surgery to repair perforation.
- Lavage abdomen and continue treatment with active drainage if possible.
- IV with broad-spectrum antibiotic.
- If renal damage is suspected:
  - Treat acid-base and electrolyte imbalances.
  - Fluid therapy with crystalloid fluid typically corrects acid-base problems; administer sodium bicarbonate if severe anemia; treat hyperkalemia, if present.
  - Continue crystalloid fluids to maintain urine production (2-3 mL/kg/hr in dogs and 1 mL/kg/hr in cats). Administer furosemide and mannitol.
  - Monitor blood pressure, urine output and CVP.
  - Protect the gastrointestinal tract by administering sucralfate to dogs and cats; administer misoprostol to dogs only for ulcer protection; administer omeprazole to dogs only.

DECONTAMINATION

Gastrointestinal exposure

- If ingestion was within two to four hours and signs are not present, induce emesis.
- If ingestion was within two to four hours and signs are present, perform gastric lavage.
- Administer activated charcoal and saline cathartic and repeat as required every four to six hours.
- Support hydration and maintain blood pressure and urine output with fluid therapy.

NOTES REGARDING GASTROINTESTINAL DECONTAMINATION

Emesis

In general, the earlier emesis is induced, the better. If the ingested dosage is not likely to cause significant symptoms, decontamination may not be necessary. Drugs that dissolve quickly and are rapidly absorbed (like some NSAIDs) require emesis in the first 30-90 minutes to be useful.
Induce emesis if:
- Ingestion occurred within the past hour.
- The patient is conscious and alert.
- The toxin is not a corrosive agent like an acid or alkali or a petroleum distillate.

Do not induce emesis if:
- The toxin was ingested more than one hour ago (this is a general guide; see specific toxin for more detail).
- The pet is weak or ill.
- The pet is exhibiting signs of hyperexcitability (toxin-induced CNS effects are associated with increased risk of seizures).
- The toxin is unknown, or is an acid, alkali, or petroleum distillate.

Induce emesis with:
- Syrup of ipecac (usually in a 7 percent solution) is a gastric irritant and stimulates the chemoreceptor trigger zone. Administer syrup of ipecac 1 to 2 mL/kg orally in dogs, not to exceed 30 ml (2 Tablespoons) or 3 mL/kg orally in cats. Syrup of ipecac should not be administered to a pet at home. The syrup should only be used once because repeated dosages have the potential to be cardiotoxic. Vomiting should begin in about 10 to 15 minutes. If the pet does not vomit within 20 to 30 minute, repeat the dose one time only.

Gastric lavage

Gastric lavage is used in cases where emesis is contraindicated (animals experiencing seizures, for example). In most cases, however, recovery of ingested materials is less from gastric lavage than emesis. Gastric lavage is effective in removing gastric contents, but is likely not very useful more than one to two hours after ingestion (this is a general rule; see specific toxin for detail), as the stomach may be empty. It is best to use a scout radiograph, if available, to assess the amount in the stomach. If nothing is seen, there is no need to assume the risks associated with gastric lavage.

The main advantage of gastric lavage is its very rapid removal of gastric contents. Caustic substances are diluted and removed, without re-exposure of the esophagus to the toxin. It also allows the introduction of activated charcoal into the stomach in pets that are otherwise uncooperative. The main disadvantages of gastric lavage are that it requires general anesthesia, risks trauma to the esophagus and stomach, risks the pet’s aspiration of charcoal or lavage fluids, and is often not able to remove undissolved or undigested parts of tablets.

Gastric lavage must be performed under general anesthesia, unless the patient is comatose. Use a cuffed well-lubricated endotracheal tube (the largest bore gastric tube that can be comfortably used) Warm water should be instilled by gravity (a dosage of 4-8 ml/kg); patient’s head should be lower than the stomach. Flush until the returning liquid is clear.

Activated charcoal

Activated charcoal is the most commonly used adsorbent, and is indicated for ingestion of large organic molecules, but not effective for heavy metals and small molecules such as methanol or ethylene or ethanol. Emesis or lavage should be followed with repeated doses of activated charcoal. With NSAID poisoning, this is particularly important as it interrupts the enterohepatic recycling of these drugs.

Charcoal can be free fed, syringed or administered by nasoesophageal, nasogastric or orogastric tube. Some patients will tolerate administration by stomach tube (gavage). Dosage is typically 1-3 g/kg (for kittens and puppies, 1-3 mg/g). For most NSAIDs, the dose will need to be repeated (use half the original dose) every six to eight hours to reduce the drug’s half-life. This is also useful with drugs that are extended-release.

If gastric lavage is performed, instill activated charcoal before the stomach tube is removed. If mixing activated charcoal with food, do not use too much food or it will reduce the charcoal’s effectiveness. If the animal is unable to keep it down, a smaller dose may be helpful.

Activated charcoal has been associated with hypernatremia, as many charcoal preparations draw water into the gastrointestinal tract. Signs of hypernatremia include ataxia, tremors, seizure and coma. Monitor the animal for these signs for a period of four hours after administering charcoal. To treat hypernatremia, start use of low sodium fluids or use warm-water retention enemas to drop serum sodium levels rapidly in acute cases. In animals with gastrointestinal erosions, charcoal may inhibit healing of lesions.
Cathartics

While little data supports the effectiveness of cathartics for toxin-removal, most sources still encourage their use as decreased gastrointestinal transit time suggests more limited absorption of the toxin. Cathartics work a number of ways. Sorbitol, for example, works osmotically, pulling free water into the gastrointestinal tract. Often used with charcoal, repeated doses of sorbitol can increase the risk of hypernatremia.

Saline cathartics stimulate gastrointestinal motility. These include sodium sulfate (also known as Glauber salts) and magnesium sulfate (Epsom salts). The recommended dose is typically 250 mg/kg mixed in water or activated charcoal. Sodium sulfate should be mixed with 5-10 times as much water and administered orally. Cathartic doses are usually repeated every two to four hours. Nausea, cramping and vomiting may occur after administration. Do not use cathartics containing magnesium with any toxins that cause CNS depression.

- Do not use cathartics containing magnesium with any toxins that cause CNS depression.
- Do not use oil-based cathartics as they decrease the effectiveness of activated charcoal and may even enhance absorption of some toxins.
- Do not use osmotic cathartics like sorbitol if the animal is dehydrated.

Aspirin (salicylate) is one of the most commonly used drugs in the United States and around the world. It is found in many prescription and non-prescription formulas. Aspirin toxicity can result from a large one-time dose or a number of small doses over a period of time. Because aspirin is considered so safe and effective, many pet-owners are not aware of the risks associated with their pet’s aspirin ingestion.

Another reason aspirin toxicity is so common is that aspirin is found in so many different kinds of preparations, including Alka-Seltzer, wart/corn remover and dozens of liniments and creams used to relieve muscle pain. (It may also be referred to as methyl salicylate, or “oil of wintergreen”). Often found in combination with other drugs, it is mixed with non-prescription strength medications like ibuprofen or acetaminophen, as well as prescription medications such as opioids. It is most commonly taken orally for analgesic, antipyretic or anti-inflammatory purposes.

Pepto Bismol contains 8.7 mg of aspirin per milliliter, meaning that two tablespoons of Pepto-Bismol contain the same amount of aspirin as a 5-grain tablet. Toxic signs in dogs and cats can be seen at doses as small as 7 mL/kg/day of Pepto-Bismol. Owners commonly give this medication to pets to treat diarrhea or stomach distress, and can easily administer higher than recommended doses. Baby and children’s formulas also encourage confusion and misuse by pet owners. Emphasize to pet owners that aspirin dosage must always be based on the weight of the animal. Additionally, flavored or coated formulas or those combined with gum can be appealing to cats and dogs, leading to accidental poisoning.

Clinical signs

The most common clinical sign of aspirin poisoning in companion animals is gastrointestinal toxicity. This may be indicated by decreased appetite, emesis, hematemesis, abdominal pain, diarrhea, melena, superficial erosion, hemorrhage, ulceration, perforation, inflammation, stricture and/or protein-losing enteropathy.

The first clinical signs are usually seen within four to six hours after ingestion of a toxic dose. They include depression, nausea, vomiting, anorexia, lethargy, metabolic acidosis, tachypnea (caused by initial respiratory alkalosis and eventual metabolic acidosis), seizures, hyperthermia and coma. Vomit may be tinged with blood due to gastrointestinal ulceration. Depression causes muscle weakness and ataxia (lack of coordination of muscle movements). Coma and death may occur within as short a period as one day.

Gastrointestinal ulceration or perforation is typically seen following the administration of repeated doses over a period of several days. Research studies of beagles receiving 250 mg aspirin three times a day for 30 days were shown to develop ulcerative or hemorrhagic gastric lesions. Anemia, bone marrow depression, Heinz body formation (in cats) and toxic aspirin-induced hepatitis may occur.

High doses of aspirin stimulate the respiratory center, causing initial respiratory alkalosis, and may also cause hyperglycemia and glycosuria. The prognosis for acute or chronic toxicosis depends on the dosage, length of time over which the dosage was ingested or administered, and the time before therapeutic intervention was begun. Aggressive intervention can be effective. Monitor the animal frequently after treatment to ensure that healing occurs or determine whether injuries are permanent.

Action mechanism

Aspirin works by blocking COX-1 and COX-2 pathways, preventing prostaglandin creation. While it reduces inflammation, fever and minor aches and pains, it also reduces renal blood flow, with potential to cause renal insufficiency with continued use. Aspirin can also irreversibly affect the action of thromboxane, which is necessary for platelet aggregation (blood clotting). Dosage of as little as 3 mg/kg given every sixth day in dogs has been shown to inhibit platelet function. Toxic doses for dogs are greater than 50 mg/kg/day and cats greater than 25 mg/kg/day.
Plasma elimination of aspirin is dependent on hepatic metabolism and the conjugation of salicylic acid with glucuronic acid. Because cats are naturally deficient of glucoronate, elimination is particularly prolonged in cats. The biological half-life at a dose of 25 mg/kg/day is seven to eight hours in dogs and 38 to 45 hours in cats.

### Treatment notes

The stomach should be emptied by inducing emesis or gastric lavage within two hours of ingestion. Some studies suggest that gastric evacuation may be of value as long as 12 hours after ingestion of coated aspirin formulations. Multiple dosings of activated charcoal can effectively block enterohepatic recirculation. It is critical to monitor the animal for hypovolemia and dehydration and restore to normal to avoid the risk of renal failure. Acid-base balances should be addressed and corrected as needed. Diuresis should begin. Intravenous fluids can facilitate perfusion of target organs. Gastric ulceration or perforation should be treated as needed.

Symptoms of anemia suggest the potential for hemorrhagic or perforating gastric ulcers. Animals presenting these symptoms may require blood transfusions or in certain cases, surgical procedures to repair. Endoscopy can be effective in locating and examining ulcers and hemorrhagic areas in the stomach. Ongoing, severe blood loss is marked by a packed cell volume of less than 20 percent, a plasma protein concentration less than 3.5g/dL, and acute blood loss of more than 30 percent of the blood volume.

Animals with severe anemia and blood loss can receive whole blood transfusions or blood replacement therapies that facilitate oxygen-carrying support. These products enhance circulatory volume and provide tissues with immediate oxygen delivery.

Immediately stop all administration of aspirin products to restore the normal production of mucosal protection of lesions and allow ulcers to heal. Many drug therapies facilitate gastrointestinal healing of ulcers, such as histamine H2 receptor antagonists, including cimetidine, famotidine and ranitidine; a proton pump inhibitor, such as omeprazole; sucralfate (aluminum salt of sucrose sulfate); and PGE1 antagonist, such as misoprostol. The proton pump inhibitor was reported successful in a treatment of a dog with gastric ulcers when many other gastric protectants used had failed. In another study, dogs with aspirin-induced gastric ulcers responded well to the use of sucralfate and cimetadine. Canine studies have also shown that misoprostol can be effective in preventing the development of aspirin-induced gastrointestinal ulcers and encourage healing.

### EMERGENCY TREATMENT

#### Procedures
- Clear airway and ventilate the patient, if necessary.
- Administer supplementary oxygen.
- Collect blood for labwork.
- Administer fluids to support blood pressure and perfusion.
- Control seizures.
- Treat hyperthermia.
- Treat pulmonary edema.

#### Decontamination
- Induce emesis or perform gastric lavage.
- Administer activated charcoal.

#### Other indications
- Administer fluids to initiate brisk diuresis. Observe carefully for possible pulmonary edema.
- Watch and treat increased intracranial pressure if suspected.
- Correct electrolyte and acid-base imbalances with slow administration of sodium bicarbonate. Hypokalemia should be addressed, as potassium affects alkalinization.
- Check glucose.
- Protect the gastrointestinal tract by administering sucralfate and misoprostol (for ulcer prevention). Administer omeprazole to dogs only.

#### Further elimination
- Urinary alkalinization can encourage urinary excretion.
- Hemodialysis is preferred.
- Hemoperfusion removes aspirin, but does not correct electrolyte and acid-base irregularities.
Acetaminophen comes in many prescription and nonprescription forms, and is combined with dozens of other medicines, including decongestants and antihistamines in cold or allergy medicine and opioids and analgesics for pain. It typically ranges from 80 mg children’s strength tablets to adult extra strength, at 500 mg. While it is very safe for humans if used in the appropriate dosage, companion animals are far more sensitive to its harmful effects. Because of its very narrow margin of safety in companion animals, acetaminophen is typically not prescribed for use in dogs and cats.

Hospital data suggests that well-intentioned owners commonly poison dogs though chronic use of therapeutic doses. Let pet owners know about the risks of administering acetaminophen to dogs and cats, as this fact is surprisingly not well known among the pet-owning public. While dogs can usually tolerate doses up to 100 mg/kg, some have shown toxicity with 150-200 mg/kg. Doses exceeding 200 mg/kg are toxic with signs including cyanosis (caused by methemoglobinemia) dyspnea, facial edema, hypothermia and vomiting, with potential progression to coma or death. Small dogs can experience significant tissue damage from as little as two regular-strength tablets. Cats are even more sensitive to acetaminophen than dogs, with toxicosis reported at dosages as low as 10 mg/kg in cats.

The prognosis for animals depends on the amount ingested and the time elapsed after ingestion and the time until treatment. Cats treated within the first 14 hours of exposure generally survive as do dogs that receive treatment no later than 72 hours. The earlier the detection and the start of antidotal therapy and supportive care, the more positive the diagnosis.

**CLINICAL SIGNS**

### Dogs

Dogs display characteristic signs of gastrointestinal distress including nausea, vomiting, abdominal pain, tachypnea, tachycardia and may show signs of jaundice. Acute signs in dogs are often related to hepatic damage. In cases where methemoglobinemia (a blood disorder in which an abnormal amount of hemoglobin builds up in the blood) is seen, hematuria, hemoglobinuria, cyanosis and paw and facial edema (characteristic of acetaminophen poisoning) may be observed. Methemoglobinemia is seen only at higher toxic dosages in dogs. Repeated use of acetaminophen cause ulcers and damage the kidneys. Dogs with prostaglandin-dependent conditions associated with heart, liver or kidney disease, diarrhea, diabetes mellitus or urinary obstruction have reduced tolerance.

### Cats

Symptoms of acetaminophen poisoning are listlessness, difficulty breathing, gastrointestinal distress and darkened urine. Clinical signs for cats do not include the hepatotoxic (hepatic toxicity) signs seen in dogs, but may include depression, vomiting, hypothermia, respiratory distress, muddy mucous membranes, cyanosis and edema of the face and paws. Hepatotoxicity in cats is usually seen only in males who have ingested a very high dosage. Acute signs in cats are often associated with methemoglobin formation.

Acetaminophen should never be consumed by cats. As little as two extra-strength tablets of acetaminophen can cause clinical signs of poisoning.

### Action mechanism

Acetaminophen is primarily metabolized by the liver and kidneys. It is absorbed nearly completely from the gastrointestinal tract and excreted primarily through the bile. Acetaminophen is poorly protein bound and widely distributed throughout the body. Both dogs and cats metabolize the drug poorly. In dogs, the liver is targeted and susceptible to injury, while in cats, red blood cells (RBC) are most prone to injury. Cats are far more prone to acetaminophen toxicosis than dogs, showing signs at dosages as low as 10 mg/kg. Methemoglobinemia appears much earlier and is more characteristic in cats than in dogs, and is typically responsible for acute signs in cats.

Acetaminophen is typically eliminated through glucuronidation and sulfation. Both are metabolic processes in which the glucuronide or sulfate combines with a toxic agent to facilitate the agent’s excretion. Both pathways are limited in cats, while only the sulfation pathway is limited in dogs. For this reason and the fact that feline hemoglobin is composed of eight sulphydryl groups (unlike the dog’s four), feline RBC are far more prone to oxidative injury.

When acetaminophen cannot be eliminated through glucuronidation and sulfation, it is broken down into a toxic metabolite called NAPQI (N-acetyl-para-benzequinoneimine). NAPQI is a free radical that damages hemoglobin, causing severe oxidative stress. NAPQI binds to the hepatic cell membrane, causing liver cell injury and death. The damage results in methemoglobin and eventual anemia. Comparing a drop of the pet’s blood next to a drop of normal blood on white filter paper shows that blood containing excess hemoglobin (methemoglobinemia) appears brownish in contrast to normal blood.
In both dogs and cats, the action mechanism of toxicosis is the depletion of cellular glutathione. Without this, acetaminophen metabolites bind to cellular proteins, damaging cell membranes through lipid peroxidation. Methemoglobin is formed when glutathione levels are exhausted. Clinical signs associated with methemoglobinemia occur when methemoglobin levels reach 20 percent of the total hemoglobin concentration. As methemoglobin levels increase, decreased oxygen delivery causes tachycardia, tachypnea, vasoconstriction and shock.

**Treatment notes**

Acetaminophen is rapidly absorbed, reaching peak blood levels within one-half to one hour. Emesis should be performed as soon as possible after ingestion, and a saline cathartic agent should be administered. Steroids should be avoided as they have been reported to increase mortality. Treatment of companion animals after consumption of acetaminophen is highly dependent on time elapsed since ingestion.

For dogs, evaluate/monitor and induce emesis if ingestion occurred within two to four hours. After four hours, gastric absorption is likely complete so emesis has no value. Within the four-hour period after emesis, administer activated charcoal (2 g/kg orally) to prevent additional absorption (after six hours, activated charcoal has little value).

Toxic metabolites prefer to bind with glutathione, so a glutathione precursor is a critical part of treatment, and traditionally considered the antidote for acetaminophen poisoning. To protect cellular glutathione, a 10 or 20 percent sterile solution of N-acetylcysteine is administered at a dose of 140 mg/kg IV or orally every six hours. N-acetylcysteine can also be given undiluted or in a 5 percent dextrose solution. N-acetylcysteine provides the cysteine for glutathione synthesis and increases serum sulfate levels, which provide sulfate for conjugation.

Anecdotal evidence suggests sulfur donors such as S-adenosylmethionine may be useful in dogs and cats. Suggested dosage in dogs is 40 mg/kg orally followed by 20 mg/kg orally every 24 hours for four days. A recommended dosage for cats has not been established; however, experimental models showed protective benefits with 180 mg orally two times daily for three days, followed by 90 mg orally two times daily for an additional 14 days.

**Cats**

For cats, if spontaneous vomiting has not begun and ingestion was less than four hours earlier, induce emesis unless contraindicated by other conditions. Gastric lavage is less effective, but may be useful if emesis is contraindicated or ineffective. Activated charcoal should be administered a number of times because acetaminophen undergoes enterohepatic recirculation, meaning compounds secreted in the bile are reabsorbed from the small intestine, causing an increase in the half-life of drugs. After administering activated charcoal, provide a cathartic if the cat is not experiencing life-threatening signs. Most activated charcoal also contains a cathartic, like sorbitol, which should be administered with every third charcoal dose.

In critical cases, stabilization is the first priority. Administer oxygen if the cat is dyspneic. IV therapy should be used to address shock and promote diuresis to encourage elimination of the toxin. Corticosteroids and antihistamines are contraindicated. Cats having difficulty breathing should be limited in their physical activity and treated gently, with as little stress as possible.

If acetaminophen poisoning is suspected, supportive therapeutic care should begin immediately. Supportive therapy includes the administration of fluids to maintain hydration and electrolyte balance. If there are signs of anemia (packed cell volume drops), administration of whole blood, packed RBC, oxygen or blood substitutes may be advisable. Both have been shown useful in improving blood’s oxygen-carrying capacity in severe cases of acetaminophen toxicosis. Some hospitals discuss successful use of oxyglobin for treatment of hypoxemia and hypovolemia but use caution to avoid the complication of volume overload with oxyglobin administration].

Ascorbic acid may facilitate conversion of methemoglobin to oxyhemoglobin. The recommended dose of ascorbic acid is 30 mg/kg every 6-12 hours orally or by IV. Some veterinarians use a combination of cimetidine with NAC and ascorbic acid, which has proven more effective than any single agent in minimizing the hepatotoxicity that occurs with acetaminophen poisoning. Do not use methylene blue as it has the potential to induce methemoglobin formation in cats and is associated with Heinz body formation and hemolysis. Heinz body formation is a change in the usual nature of hemoglobin in RBCs that results from oxidative injury.

Methemoglobinemia or hepatic injury development can be mediated by administration of N-acetylcysteine (NAC), which binds with NAPQI, enhancing elimination, minimizing cell injury and functioning as a glutathione precursor. NAC is administered at a loading dose of 140-280 mg/kg orally or by IV every four hours for a minimum of three to five treatments. NAC should be diluted to a 5 percent solution before administration. Given the extended half-life of acetaminophen in cats, NAC should be administered to cats with clinical signs regardless of the length of time since the medication was consumed.

An alternative to N-acetylcysteine is sodium sulfate at 50 mg/kg of 1. 60 percent solution given by IV every six hours (four treatments). Treatment is encouraged up to 18 hours after ingestion because antidotal treatment and supportive care continue to show positive results.
Cimetidine is an H2 receptor antagonist that inhibits cytochrome P-450 oxidase in the liver and may help facilitate the metabolism of acetaminophen to NAPQI. Cimetidine dosage is 5-10 mg/kg orally, intramuscularly, or by IV every six to eight hours. Use caution with geriatric pets or those with impaired hepatic or renal function. To address acetaminophen-related hepatic injury in the long term, some have found S-adenosylmethionin helpful in a dose of 18 mg/kg for one to three months.

Hepatic damage may take weeks of attention to treat. The prognosis is highly dependent on how quickly the cat received treatment, the dose and the severity of clinical signs. Cats with severe signs of methemoglobinemia or hepatic damage have poorer prognoses.

Cats eating wet food eat a diet high in propylene glycol (7-13 percent in wet food), which may cause methemoglobinemia or Heinz body formation in cats. This factor can make cats more sensitive to red blood cell oxidative stress caused by acetaminophen consumption.

Cimetidine

**Procedures**

- Clear the airway and ventilate, if necessary.
- Administer supplementary oxygen.
- Collect blood for labwork.
- Administer fluids as needed to support blood pressure and perfusion.
- Add active hemoglobin and increase oxygen delivery.
- Control seizures.

**Decontamination**

- Induce emesis (unless animal is weak or otherwise contraindicated), or perform gastric lavage.
- Administer activated charcoal and repeat every three to four hours. However, If N-acetylcysteine is to be given orally, delay active charcoal. See below.
- Administer saline or osmotic cathartic agents.

**Other indications**

- N-acetylcysteine (Mucomyst): for dogs: 280 mg/kg loading dose orally followed by 140 mg/kg for following treatment; for cats: 140-240 mg/kg oral loading dose in cats, followed by 70 mg/kg for further treatments. N-acetylcysteine can be use IV either full strength or diluted in Dextrose but must be handled in a sterile manner and infused though a filter. If the pet is conscious, the oral route is preferred because it is rapidly absorbed from the gastrointestinal tract, where it enters portal circulation. This is assumed to increase the amount of drug presented and utilized by the liver.
- Administer fluids to maintain hydration and urine output.
- Treat increased intracranial pressure, if suspected.
- Ascorbic acid may supplement the action of glutathione and may be effective in converting methemoglobin to oxyhemoglobin.
- With severe acidosis, use bicarbonate.
- Cimetidine may also be helpful.
- With severe liver condition may require the use of fresh or frozen plasma.
- Hemoperfusion has been shown to facilitate elimination of acetaminophen.
- Cats that survive subtoxic doses may die suddenly if administered an additional acetaminophen dose.

**Ibuprofen (Advil and Nuprin)**

Ibuprofen is derived from propionic acid and has many of the analgesic, anti-inflammatory and antipyretic effects characteristic of NSAIDs. Common brand names for ibuprofen include Advil, Midol and Motrin. Ibuprofen is also available in generic forms. It is commonly used for both short-term pain management and long-term chronic symptoms. It is available in a variety of strengths, in liquids, tablets and capsules. It often is combined with other medications, including pseudoephedrine hydrochloride or hydrocortisone birartrate.

In humans, ibuprofen in non-prescription strength has a wide margin of safety, with fewer side effects than with the same doses of aspirin. In dogs and, cats, however ibuprofen is more of a risk, with dog poisonings from ibuprofen the most common toxicosis reported to the ASPCA Poison Control Center. In most cases, exposures were acute, due to the large number of tablets taken. Anecdotal evidence suggests dogs enjoy chewing on plastic bottles. If they are able to get to the pills, they are likely to enjoy the sweet coating on many ibuprofen tablets. In some cases, animals are given small amounts of ibuprofen by their owners to treat chronic conditions. Stress to pet-owners how sensitive companion animals are to ibuprofen, with even very low doses (8 mg/kg/day) producing gastric lesions in dogs. Cats are typically two times as sensitive as dogs to ibuprofen, with clinical signs of poisoning at 50 mg/kg body

EMERGENCY TREATMENT

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Because ibuprofen has the potential to cause multiorgan toxicities and a long list of potentially adverse effects, its use is never recommended in companion animals.

**Clinical signs**

Acute overdose in dogs and cats is associated with gastrointestinal, renal and central nervous symptoms. Vomiting, abdominal pain, hematemesis and diarrhea are common within 24 hours of ingestion. Vomiting, diarrhea, nausea, anorexia, gastric ulceration and abdominal pain are seen with doses of 50-125 mg/kg in dogs. These signs in combination with renal damage are seen at doses at or about 175 mg/kg, while doses at or above 400 mg/kg show central nervous system (CNS) effects such as seizure, ataxia and/or coma. Cats are considered to have two times the sensitivity to ibuprofen as dogs due to more limited glucuronyl-processing ability, which results in greater toxicity. The effects are similar to acetaminophen, but ibuprofen metabolizes more slowly, increasing the risk of toxic levels.

Clinical signs of ibuprofen toxicity for dogs and cats are gastrointestinal and renal, and include nausea, vomiting, abdominal pain, gastrointestinal ulceration, renal compromise, mild CNS depression, blood in the stool, staggering, increased thirst, listlessness, increased frequency of urination and seizures. It can also cause liver and kidney disease. The severity of symptoms will depend on the amount ingested and the period of time elapsed since ingestion. Ibuprofen undergoes extensive enterohepatic recirculation.

Younger animals may metabolize the drug more slowly and show delayed clearance.

A single dose as low as 25 mg/kg can cause vomiting in dogs. At larger doses, the risk of acute renal failure in dogs and cats escalates, as prostaglandins responsible for vasodilation and maintenance of the renal medulla’s blood flow fail. Reduced blood flow may trigger acute interstitial nephritis, papillary necrosis, renal-tubular necrosis and acute renal failure. Existing renal disease and hypovolemia, which can be exacerbated by vomiting and dehydration, increase the risk of renal toxicity from ibuprofen.

**Ibuprofen dose and associated symptoms/outcomes in dogs**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Symptom/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-125 mg/kg</td>
<td>Vomiting, diarrhea, nausea, abdominal pain, anorexia.</td>
</tr>
<tr>
<td>Over 175 mg/kg</td>
<td>All of the above as well as hematemesis, melena, polyuria or polydipsia, oliguria, uremia and acute renal failure.</td>
</tr>
<tr>
<td>Over 400 mg/kg</td>
<td>All of the above as well as seizures, ataxia, coma and shock.</td>
</tr>
<tr>
<td>Over 600 mg/kg</td>
<td>Death.</td>
</tr>
</tbody>
</table>

**Action mechanism**

While not fully understood, it is suggested that ibuprofen inhibits the conversion of arachidonic acid into certain prostaglandins by temporarily blocking the actions of cyclooxygenase (COX) enzymes. Elimination occurs though hepatic biotransformation, causing inactive metabolites to be filtered and excreted by the kidneys. About three-fourths of the drug is excreted in the urine as metabolites, with the rest excreted through feces. Significant enterohepatic circulation occurs in both dogs and cats.

**Dogs**

Ibuprofen has a narrow margin of safety in dogs. While recommended dosages are commonly around 5 mg/kg/day (divided), signs of toxicosis have been seen with dosages of 8 mg/kg/day for a 30-day period. While no clinical signs were apparent at this dosage, research data shows dogs developed gastric ulcers and intestinal inflammation. In the same study, dogs consuming 16mg/kg/day experienced vomiting, diarrhea, melena and weight loss by the eighth week of drug administration. Another study presents evidence of a dog with fatal gastric perforation after a period of six weeks consuming 3 mg/kg every other day. Long-term administration can be complicated by renal insufficiency or failure, impaired hepatic function, hypoalbuminemia, stress (such as a recent surgical procedure), all of which reduce the dog’s tolerance of the drug. Additionally concurrent administration of medications such as glucocorticoids may also increase ibuprofen toxicity.

**Treatment notes**

After acute ibuprofen overdose, fast and aggressive decontamination is critical. If the animal is not vomiting or showing neurologic signs, emesis should be attempted, ideally within two hours of ingestion. Animals exhibiting neurological signs are not candidates for emesis. Instead, gastric or enterogastric lavage may be useful. Administer doses...
of activated charcoal in all affected animals every six to eight hours for a period of 24 hours to address ibuprofen undergoing enterohepatic recirculation.  

Other treatments must address potential complication of acute or chronic exposure to ibuprofen. Gastrointestinal protection should be used to address gastrointestinal distress and possible ulceration. For doses under 100 mg/kg, use OTC liquid antacids with aluminum, or magnesium hydroxide may be used. DO NOT use any product that contains bismuth subsalicylate, such as Pepto-Bismol or some forms of Kapectate, due to its potential interaction with the ibuprofen.  

In cases where gastrointestinal signs exist (typically over 100 mg/kg), the combined use of acid reducers such as H2-blockers or proton pump inhibitors, sucralfate, and misoprostol may be useful. Treatment should continue for one to two weeks, depending on symptoms. Vomiting can be controlled with an entemtic. Transfusions may be necessary for animals with severe gastrointestinal bleeding. Perforations may need to be treated surgically. At higher doses (above 175 mg/kg), with the potential to cause renal failure, diuresis with intravenous fluids (given at 2 times the daily maintenance rate of 120 ml/kg/day) for a period of 48 hours is recommended. Check blood urea nitrogen, creatinine and phosphorous levels and compare with baseline values. Urinalysis can be used to check for tubular casts (can be seen in as few as 18 hours). If renal function is normal at 48 hours, fluids can be reduced to maintenance rates and discontinued after 24 hours if renal values are normal. For elevated results, continue diuresis until values return to normal. Treat neurological symptoms, as needed. Seizures can be controlled with diazepam or barbiturate. Comotose pets will require supportive care. Monitor and maintain body temperature and respiratory support.

References

3. Roder 2005
5. Adapted from Fitzgerald, 2006.
9. Gfeller and Messonnier 2004
10. Fitzgerald, Kevin T PhD, DVM , DABVP, Alvin C. Bronstein MD FACMT, a nd Aryn Veterinarians.EliteCME.com
16. Steenbergen 2003
23. TAlcott 2006.
28. Richardson 2000
30. Steenbergen 2003
32. Richardson 2000.
34. Richardson 2000
38. Richardson 2000
39. Richardson 2000
40. Richardson 2000
42. Steenbergen 2003
46. Richardson 2000
49. Osweller 1997
50. Richardson 2000
51. Richardson 2000
52. Richardson 2000
54. Richardson 2000
57. Richardson 2000
59. Richardson 2000
60. Beasley 1999.
61. Richardson 2000
72. Talcott 2006
76. Ibuprofen, AHFS Drug Information 2001
81. Villar 1998
82. Dunayer 2004
83. Richardson, 2000
84. Villar 1998
85. Richardson 2000
86. Villar 1998
1. Cyclooxygenase is an unsaturated fatty acid responsible for converting arachidonic acid into prostaglandins, which are required for many normal body functions.
   - True
   - False

2. NSAIDs tend to be more toxic in humans than cats and dogs.
   - True
   - False

3. Do not induce emesis if the toxin is unknown, or is an acid, alkali or petroleum distillate.
   - True
   - False

4. Hydrogen peroxide should be used with extreme caution in dogs as they are more sensitive to hemorrhagic gastritis.
   - True
   - False

5. Signs of hypernatremia include ataxia, tremors, seizure and coma.
   - True
   - False

6. Sodium sulfate is also known as Epsom salt.
   - True
   - False

7. Do not use saline cathartics as they decrease the effectiveness of activated charcoal, and may even enhance absorption of some toxins.
   - True
   - False

8. Aspirin can irreversibly affect the action of thromboxane, which is necessary for platelet aggregation (blood clotting).
   - True
   - False

9. The biological half-life of a dose of 25 mg/kg/day aspirin is seven to eight hours in dogs and 38-45 hours in cats.
   - True
   - False

10. Cats are even more sensitive to acetaminophen than dogs, with toxicosis reported at dosages as low as 10 mg/kg in cats.
    - True
    - False