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in dogs and cats

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The 10 most common toxicoses in dogs

Irina Meadows, DVM, and Sharon Gwaltney-Brant DVM, PhD

Dogs are usually exposed to potentially toxic household products and medications accidentally. But sometimes well-intentioned owners unknowingly give their dogs harmful products and medications. To help prepare you for patients with theses toxicoses, we compiled this list of the 10 most common hazards to dogs, based on the number of calls we have received at the ASPCA Animal Poison Control Center (APCC) between 2001 and 2005.[1]

Ibuprofen

Ibuprofen, a nonsteroidal antiinflammatory drug with analgesic, anti-inflammatory, and antipyretic effects,[2] is available in a variety of strengths. The most common over-the-counter strength is 200 mg, but the prescription-strength tablets can contain up to 800 mg ibuprofen. Ibuprofen has a narrow margin of safety in dogs, and acute toxicosis is common. Dogs are often exposed to ibuprofen accidentally when they chew on a medicine bottle, but sometimes owners give ibuprofen to their dogs intentionally for pain control.

Ibuprofen overdose can cause GI, renal, and central nervous system (CNS) effects. Doses of 25 mg/kg or more often lead to gastrointestinal (GI) problems and ulceration, manifested as vomiting, diarrhea, or abdominal pain. Doses approaching 175 mg/kg increase a dog's risk of developing acute renal failure,[2] but older dogs or those with preexisting renal compromise may exhibit renal failure at lower doses. With doses greater than 400 mg/kg, CNS effects such as depression, seizures, and comas may occur.

Treatment for acute ibuprofen toxicosis includes inducing emesis, administering activated charcoal (multiple charcoal doses are indicated to reduce enterohepatic recirculation in dogs that have ingested high doses of ibuprofen) and GI protectants (H_2-blockers, sucrafate, misoprostol), and inducing diuresis with intravenous fluids at twice the maintenance rate while monitoring renal function. With timely and apprpriate treatment, most dogs are expected to have a positive outcome.

Chocolate

Chocolate contains two types of methylxanthine, theobromine and caffeine, with their amounts varying depending on the type of chocolate. For example, milk chocolate contains about 60 mg/oz methylxanthine, dark chocolate about 150 mg/oz, and baking chocolate about 450 mg/oz.[3]

Clinical signs of chocolate

ingestion range from GI upset to cardiovascular effects (*e.g.* tachycardia, hypertension or hypotension, arrhythmias) to CNS signs (*e.g.* agitation, pacing, hyperactivity, tremors, seizures). The toxicity depends on the type of chocolate, the amount ingested, the size of the animal, and the animal's sensitivity to methylxanthines. Mild stimulation such as hyperactivity, agitation, and restlessness may occur in dogs ingesting around 20 mg/kg methylxanthine. Cardiotoxicosis may occur in dogs ingesting 40 mg/kg, and dogs ingesting more than 60 mg/kg may exhibit severe CNS signs, such as tremors and seizures.[3] GI signs such as vomiting and diarrhea can occur with any amount because of chocolate's high fat and sugar content.

Treating chocolate ingestion includes inducing emesis or performing gastric lavage, administering activated charcoal (multiples doses are recommended with large ingestions), monitoring the patient's vital signs closely, and providing supportive care. Continous electrocardiogram (ECG) monitoring is advisable in cases in which cardiotoxicosis is expected. Performing baseline serum chemistry profiles and monitoring electrolytes in symptomatic animals are also recommended. Dogs should be stabilized before you initiate decontamination procedures. Administer intravenous fluids to enhance methylxanthine excretion, beta-blockers (*e.g.* propranolol, metoprolol) to reduce tachycardia, and diazepam to control agitation and tremors. Methylxanthines can be reabsorbed from the bladder, so monitor urine output and consider placing a urinary catheter to keep the bladder empty. Signs can last 24 to 72 hours because of the long half-life of theobromine in dogs (17.5 hours vs. 4.5 hours for caffeine).[3]

Ant and Roach Baits

The product names may vary, and the containers may be referred to as *chambers, discs, stations, systems, traps, baits, or trays,* but most ant and roach baits use an attractant (often peanut butter), a sweetening agent, and bread. And while these baits once contained compounds that are relatively highly toxic to mammals (*e.g.* arsenic trioxide, lead arsenate), the most common insecticides used in ant and roach baits today are boric acid, avermectin, fipronil, hydramethylnon, propoxur, and sulfluramid.[1]

Because of the low concentration of the insecticide and the small size of the bait, serious toxicosis in mammalian pets ingesting the baits is not expected.[4] In many instances, the risk of foreign body obstruction from the plastic or metal part of the container is of greater concern than the active ingredients. Signs of ingestion are usually limited to mild GI upset and do not require specific treatment.

Rodenticides

The three main types of rodenticides are those containing anticoagulants (warfarin, brodifacoum, diphacinone [also called *diphenadione*]), those containing bromethalin, and those containing cholecalciferol.

Anticoagulant rodenticides are probably the most commonly used rodenticides in the world. Ingesting an anticoagulant rodenticide can block vitamin K-dependent clotting factor synthesis by inhibiting the 2,3-epoxide reductase enzyme, which results in a coagulopathy three to five days after ingestion (possibly sooner in immature animals).[5]

Ingesting a bromethalin-containing rodenticide may cause vacuolization and severe spongiosis of the white matter within the CNS and cerebral edema.[6] Bromethalin ingestion can cause signs ranging from tremors and seizures (convulsant syndrome) to weakness and paralysis (paralytic syn-

drome). Convulsant syndrome usually occurs at doses of 2.3 mg/kg and higher. Paralytic syndrome is more likely when a dog ingests a lower dose.[6]

Ingesting cholecalciferol-containing rodenticides can increase dogs' serum calcium and phosphorus concentrations, potentially leading to acute renal failure and tissue mineralization.[7]

Perform gastric decontamination procedures (induce emesis and administer activated charcoal with a cathartic) as soon as possible after any rodenticide ingestion. Do not induce emesis in symptomatic animals (*e.g.* bleeding or seizing animals).

Treat anticoagulant-rodenticide ingestion with vitamin K_1 orally for 14 to 30 days, depending on the specific active ingredient. It is recommended to evaluate the one-stage prothrombin time at 48 hours after the last dose of vitamin K_1.

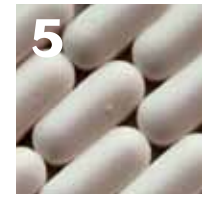
An alternative to treatment is to monitor the prothrombin time at 48 and 72 hours after ingestion, and if elevated, initiate vitamin K_1 therapy.[8] Animals that have developed a coagulopathy may require whole blood or plasma transfusion and oxygen. The prognosis for animals that have developed a coagulopathy is guarded and depends on the bleeding site.

Because no specific treatment for bromethalin toxicosis is available, aggressive decontamination is critical. If clinical signs develop, they are difficult to treat, and the patient's prognosis is guarded. Therapy is directed at resolving cerebral edema and addressing sezures, usually by administering corticosteroids, furosemide, mannitol, and diazepam. Since the cerebral edema from bromethalin toxicosis is intramyelinic,[6] it does not respond well to standard therapy. Mannitol, corticosteroids, and furosemide may temporarily lower cerebrospinal fluid pressure, but signs often progress once these treatments are discontinued.

In rats, an extract of *Ginkgo biloba* was shown to reduce the development of cerebral edema and brain lipid peroxidation when administered orally immediately after gavage with a lethal dose of bromethalin.[6] Whether *G. biloba* or its extracts would influence the development of clinical signs in dogs with bromethalin toxicosis is unknown, but you may wish to consider it in patients in which other options have been unsuccessful.

Treating cholecalciferol-containing rodenticide ingestion requires close monitoring of the serum calcium and phosphorus concentrations and the renal function parameters for 72 to 96 hours. If hyperphosphatemia or hypercalcemia occurs, perform saline diuresis, and administer corticosteroids, furosemide, or phosphate-binding agents. Salmon calcitonin or pamidronate may also be needed. Pamidronate, a bisphosphonate used in people to treat hypercalcemia of malignancy, is a preferred agent in treating cholecalciferol toxicosis.[7] Although expensive, a single dose of pamidronate is often sufficient to lower calcium concentrations enough that the animal can be returned home with minimal additional treatment.

Acetaminophen



Acetaminophen is available as tablets, capsules, or liquids, either alone or combined with other compounds such as opioids, aspirin, caffeine, and antihistamines. Acetaminophen toxicosis can result in hepatotoxicosis, methemoglobinemia, and facial and paw edema.[9] Some dogs have developed transient keratoconjunctivitis sicca after ingesting acetaminophen doses well below the amounts previously considered to be of concern.[1] Hepatotoxicosis can occur with doses of 50 to 100 mg/kg, and methemoglobinemia may occur in up to 75% of dogs ingesting 200 mg/kg.[10]

To treat acetaminophen toxicosis, initiate gastric decontamination procedures, and then administer a 5% N-acetylcysteine

(NAC) solution. Administer 140 mg/kg NAC orally as a loading dose, followed by 70 mg/kg every six hours for at least seven doses.[9] Although NAC is not labeled for intravenous administration, it can be given intravenously in life-threatening situations by using a bacteriostatic filter (0.2 µm). Administer fluid therapy to maintain hydration; diuresis does not enhance acetaminophen elimination. Adjunctive therapies include administering ascorbic acid, which helps reduce methemoglobin to hemoglobin; cimetidine, which inhibits cytochrome P-450 oxidation in the liver and may help reduce acetaminophen metabolism; and S-adenosylmethionine in patients in which long-term treatment of hepatic injury is needed. Monitor serum chemistry profile parameters, and evaluate tear production and administer artificial tears and cyclosporine if needed.[9] The facial and paw edema will resolve on its own, so corticosteroids and antihistamines are not indicated.

Pseudoephedrine-Containing Cold Medications

Many cold medications contain pseudoephedrine, a sympathomimetic drug structurally similar to amphetamines. Pseudoephedrine ingestion can lead to dose-dependent stimulation of the cardiovascular system and the CNS. The most common clinical signs include agitation, hyperactivity, panting, hyperthermia, hypertension, tachycardia, head bobbing, or mydriasis. Ingesting as little as 10 to 12 mg/kg pseudoephedrine can cause life-threatening signs.[11]

Treatment includes gastric decontamination in asymptomatic animals, patient monitoring, and symptomatic care. Agitation and hyperactivity are best controlled with acepromazine; avoid diazepam because it may exacerbate the agitation. Administer phenobarbital or pentobarbital to control severe tremors and seizures, and give isoflurane in refractory cases. Fluid therapy enhances pseudoephedrine excretion and protects the kidneys from myoglobinuria, which can result from excessive shaking. Because of likely hypertension, do not exceed fluid rates of one and a half to two times the maintenance rate unless the dog is in shock or dehydrated. Closely monitor the heart rate and rhythm, and use beta-blockers, such as propranolol, if tachycardia is severe. Signs can persist for up to 72 hours.[11]

Thyroid Hormones

Natural (desiccated thyroid) and synthetic (levothyroxine) derivatives of thyroid hormones are used to treat hypothyroidism in animals and people.

Dogs can maintain a remarkably normal physiologic state in the face of a massive L-thyroxine overdosage. Such resistance to developing thyrotoxicosis can be explained in part by pharmacokinetics, such as poor GI absorption, serum tri-iodothyronine (T_3) and thyroxine (T_4) being highly protein bound, alternative metabolic pathways, and greater potential for biliary excretion and fecal loss. In addition, certain organs (particularly the liver and kidneys) can concentrate thyroid hormones intracellularly, thereby rendering these hormones unavailable to bind to tissue receptors and induce a physiologic effect. Thus, the liver and kidneys can act as buffers by releasing small or large amounts of hormones, depending on what the body needs, back into the plasma. In an overdose situation, these buffer organs can concentrate the extra hormone and not release the already stored hormone.[12]

Dogs ingesting 0.2 mg/kg levothyroxine may develop mild signs, and dogs ingesting 1 mg/kg or more may need treatment.

Hyperactivity and tachycardia are the most common signs of thyrotoxicosis.[13]

Initiate gastric decontamination procedures in patients that ingest a large dose, and monitor the patients' ECGs, blood pressures, and serum T_4 concentrations. Treatment is symptomatic and supportive. Diazepam can be given to control hyperactivity, and beta-blockers can be given to control tachycardia.[12]

Bleach

Regular household bleaches contain 3% to 6% sodium hypochlorite; commercial bleaches are typically much more concentrated. Color-safe bleaches contain sodium peroxide, sodium perborates, or enzymatic detergents. Most household bleaches are mild to moderate irritants and are not associated with a marked degree of tissue destruction. Household bleaches can cause skin or eye irritation, mild oral or esophageal burns, or GI irritation.[14] Commercial bleaches can be corrosive and lead to severe stomatitis, pharyngitis, esophagitis, or esophageal ulcerations. Inhalation exposure to bleach can cause respiratory irritation, coughing, and bronchospasm. More serious damage can occur when bleach is mixed with ammonia-containing agents, forming chloramine and chlorine gases. Inhaling these gases can lead to a chemical pneumonitis.

To treat dermal exposure, bathe the dog with mild dishwashing detergent. The preferred initial treatment with bleach ingestion is oral dilution with milk or water. Dilution is most effective if it is performed early. Emesis is contraindicated because of the irritating properties of household bleach and the potential corrosive effects of commercial bleaches. GI protectants such as sucralfate or H_2-blockers can also be used to symptomatically treat bleach ingestion. Treating corrosive damage may also require pain medications, antibiotics, and nutritional support. Oxygen and bronchodilators may be needed to treat respiratory signs in cases of inhalation exposure.

Fertilizer

Fertilizer products generally contain varying amounts of nitrogen (N), phosphorus (P), and potassium (K) compounds. Product ingredients are often listed as *N-P-K 10-8-8,* where each number is the corresponding ingredient's concentration percentage. Fertilizer formulations include liquid, granular, and solid (*e.g.* stakes), and fertilizer additives may include herbicides, insecticides, fungicides, iron, copper, or zinc. Because fertilizers are usually a combination of ingredients, several toxic principles are possible. In general, the ingredients are poorly absorbed, and most of the signs are related to GI irritation.

Fertilizers have a wide margin of safety.[15] GI signs such as vomiting, hypersalivation, diarrhea, or lethargy are common in dogs after ingesting fertilizers, especially ones with high percentages of phosphorus and potassium compounds. In most cases these signs are self-limiting and resolve within 12 to 24 hours.[15]

Treat animals with GI signs supportively with antiemetics, fluids, and GI protectants. Address added insecticides or herbicides separately. Heavy metals, such as iron, are generally not bioavailable but can pose a hazard when dogs ingest large amounts.

Hydrocarbons

Hydrocarbons are in numerous products, including paints, varnishes, engine cleaners, furniture polish, lighter fluid, lamp oils, paint removers, and fuel oil *(e.g.* acetone, xylene,

kerosene, gasoline, naphtha, mineral oil). GI signs such as vomiting and diarrhea are common in dogs ingesting hydrocarbons. Mild to moderate eye irritation and reversible ocular injury may occur after contact with most hydrocarbons.[16] Acute but prolonged skin exposure to some hydrocarbons can result in dermal burns and, occasionally, systemic effects. Low-viscosity, highly volatile hydrocarbons (*e.g.* those found in kerosene, gasoline, liquid furniture polish) are aspiration hazards. Pulmonary damage, transient CNS depression or excitement, hypoxia, inflammation, and, potentially, secondary infection (pneumonia) can occur.[16] Hepatic and renal damage have been reported from a percentage of both experimental and field cases of hydrocarbon poisoning. Some hydrocarbons are also apparently capable of sensitizing the myocardium to endogenous catecholamines, resulting in arrhythmias and even complete cardiovascular collapse.[16]

Because of the risk of aspiration, emesis is contraindicated in patients ingesting products containing hydrocarbons. Dilution can be recommended. To treat topical exposure, bathe the dog with a liquid dishwashing detergent. Flush the eyes copiously with saline in cases of ocular exposure. Closely monitor patients for aspiration pneumonia, particularly in vomiting dogs.[16] Treatment is supportive and symptomatic. VM

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The 10 most common toxicoses in cats

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Cats are sensitive to many toxic agents, sometimes in ways unique to their species. In addition, cats are less likely than dogs to expose themselves through curious ingestions, but cats will nibble on potentially deadly agents, such as lilies. Cats also can jump to high places and obtain materials assumed to be out of reach. And because of their grooming behavior, cats with dermal exposure are likely to receive an oral dose as well.

In this article, we describe 10 common toxicoses in cats. The agents discussed were selected based on the 10 most frequent feline exposures reported to the ASPCA Animal Poison Control Center (APCC) in the past four years.

Canine Permethrin Insecticides

The topical application of a permethrin spot-on or dip product labeled for use only in dogs can lead to tremors and seizures in

cats. These products, which generally contain 45% or 65% permethrin in spot-ons and 3% or more permethrin in dips, are applied to cats accidentally or by individuals who ignore the warnings on the label. In some instances, cats have developed signs of permethrin toxicosis after being in close contact with (sleeping near or grooming) a dog recently treated with a permethrin spot-on product. Initial signs may appear within a few hours but can take 24 to 72 hours to manifest. Full body tremors are the most common finding, although seizures may also occur.[1] Other pyrethroids, including phenothrin and etofenprox, can cause a similar syndrome in cats when used at high concentrations.[2]

Treatment consists of bathing the cat in a liquid hand dishwashing detergent (*e.g.* Dawn Dishwashing Liquid—Procter & Gamble) to remove the sebum in which the product is distributed. If the cat is symptomatic, delay the bath until the tremors have been controlled. The tremors are best treated with slow intravenous boluses of methocarbamol (Robaxin-V—Fort Dodge Animal Health; total initial dose 55 to 220 mg/kg).[1] Repeat the methocarbamol as needed, but do not exceed a dose of 330 mg/kg/day or respiratory depression may occur.[3] If methocarbamol is not effective, then barbiturates, propofol, or both can be used. Diazepam is generally ineffective for the tremors but should be used if seizures are present.

Additional care should include monitoring the patient's body temperature and administering intravenous fluids to protect the kidneys from myoglobinuria due to muscle breakdown. Atropine is not antidotal for permethrin; no true antidote exists. The prognosis is

generally good with aggressive supportive care.

Other Topical Insecticides

Besides permethrin products, many other flea control products are on the market today. Topical flea control products commonly include insect growth regulators such as s-methoprene and pyriproxyfen, which have low oral and dermal toxic potential in mammals. Insecticide ingredients may include organophosphates or carbamates, pyrethroids, imidacloprid, fipronil, and selamectin, all of which when used appropriately (including low-concentration pyrethroid products) have a low risk of causing serious problems.[4,5] In general, topical flea control products applied according to label directions will not cause systemic effects in cats.[4,5] Any topically applied product can cause either dermal irritation or a dermal hypersensitivity-like reaction. If dermal signs appear, wash the product off with a mild detergent. If the irritation is localized, the contents of a vitamin E capsule or a corticosteroid cream can be applied. If the irritation is more widespread, corticosteroids or antihistamines may be used systemically.

If a cat licks a topically applied product, a taste reaction—characterized by hypersalivation, agitation, and occasionally vomiting—may develop. These signs are simply a reaction to the bitter taste and can sometimes be quite dramatic. Removing the product from the tongue by giving the cat milk or liquid from a tuna fish can should resolve the signs.

Venlafaxine

Venlafaxine (Effexor, Effexor XR—Wyeth) is a bicyclic antidepressant available in tablets and capsules of 25, 37.5, 50, 75, 100, and 150 mg. Venlafaxine acts as a serotonin and norepinephrine reuptake inhibitor as well as a weak dopamine reuptake inhibitor. Cats seem to readily eat venlafaxine capsules (ASPCA APCC Database: Unpublished data, 2003-2005). Less than one 37.5-mg capsule is enough to cause mydriasis, vomiting, tachypnea, tachycardia, ataxia, and agitation (ASPCA APCC Database: Unpublished data, 2002-2005). Signs generally begin within one to eight hours after exposure (later if an extended-release formulation was ingested).

Emesis may be initiated in asymptomatic patients. Activated charcoal is effective; repeat the dose in four to six hours if the animal was exposed to an extended-release formulation. Be sure to monitor heart rate and blood pressure. Cyproheptadine (1.1 mg/kg orally or rectally up to three or four times a day) can be used as a serotonin antagonist, and acepromazine or chlorpromazine can be used to treat agitation. Generally, the prognosis is good with close monitoring and treatment of signs.

Glow Jewelry and Sticks

Glow jewelry and sticks are plastic bracelets, necklaces, and wands that contain a liquid that glows in the dark. The jewelry is popular throughout the summer, especially around the Fourth of July and at Halloween. Cats frequently bite into the jewelry. The main ingredient is dibutyl phthalate, an oily liquid that has a wide margin of safety with an oral LD_{50} in rats of greater than 8 g/kg.[6] So ingesting the contents of a piece of glow jewelry should not cause any serious effects. The chemical has an extremely unpleasant taste, and most cats will not ingest more than a small amount. Almost immediately after biting into a piece of glow jewelry, cats exhibit signs of a taste reaction,

including hypersalivation, agitation, and, occasionally, vomiting. The behavioral changes are likely due to the cat's reacting to the unpleasant taste. A tasty treat such as milk, liquid from a tuna fish can, or other palatable food can ameliorate the taste reaction. Remove any liquid on the fur with a wet washcloth to prevent re-exposure; take the cat into a darkened room to help you identify the product on the coat.[6]

Lilies

Cats ingesting lilies can develop acute renal failure. While many plants are called *lilies*, renal failure has been seen only with *Lilium* species (*e.g.* Easter lilies, Stargazer lilies, tiger lilies, Asiatic lilies, Oriental lilies) and *Hemerocallis* species (day lilies).[7] Ingesting any part of the plant (including the pollen) may cause signs, and even the smallest of exposures should be aggressively treated.

After ingesting lilies, cats generally develop vomiting and depression within two to four hours. Often the cats seem to recover and then begin to deteriorate rapidly about 24 to 72 hours after the exposure with signs of polyuria, polydipsia, and more severe depression.[8] A serum chemistry profile reveals elevated creatinine, blood urea nitrogen (BUN), and phosphorus concentrations; the creatinine concentration is often elevated disproportionately to the BUN concentration.[7] Urinalysis may show cellular casts beginning about 18 hours after exposure.

Treatment consists of immediate decontamination, including emesis and activated charcoal. Start fluid diuresis as soon as possible, and continue it for at least 48 hours. The prognosis is good with prompt, aggressive treatment. Once renal failure develops, some recovery is possible but may take weeks, and the cat may require peritoneal dialysis for support.[7] The development of oliguria or anuria is a poor prognostic sign.[7]

Liquid Potpourri

Liquid potpourri is used as household fragrance, often placed in a bowl over a candle or heat source. Cats may lick the product from the container or from their fur if exposed to a spill. Liquid potpourri may contain high concentrations of cationic detergents, essential oils, or a combination of both.[9] Cationic detergents are corrosive to the oral mucosa and can cause severe gastrointestinal upset, drooling, central nervous system (CNS) depression, and hypotension. Cats may exhibit dermal irritation and ulceration as well as severe corneal ulceration if skin or eye exposure occurs. Essential oils may cause gastrointestinal and oral irritation and CNS depression.[9]

If the exposure is detected quickly, dilution with milk or water should be performed; do not induce vomiting or administer activated charcoal. Hospitalize symptomatic cats. Sucralfate slurries can be used to coat and protect oral and esophageal lesions while they heal. Pain management with opioids can make the cats more comfortable. Monitor the white blood cell count and begin antibiotics if signs of infection are evident. Give intravenous fluids for hydration. Cats may be anorectic for several days, so forced feeding or alimentation through a feeding tube may be needed until the cats recover. Endoscopy may be required to evaluate esophageal damage, but be sure to avoid further damage to or perforation of a devitalized esophagus. The prognosis with supportive care is good unless esophageal damage has occurred.

Nonsteroidal Anti-Inflammatory Drugs

Cats may be exposed to nonsteroidal anti-inflammatory drugs (NSAIDs) either by owner

administration or, more rarely, by self-ingestion, often with canine chewable formulations. NSAIDs can cause gastrointestinal upset, including vomiting, diarrhea, ulceration, hemorrhage, and ulcer perforation. Acute renal failure can occur at higher dosages. Some NSAIDs have been associated with CNS signs such as seizures and comas at high doses in cats. The more common drugs that can cause this syndrome include carprofen, ibuprofen, deracoxib, naproxen, etodolac, meloxicam, and indomethacin.[10,11]

In general, cats have a low tolerance for NSAIDs. For example, cats are thought to be at least twice as sensitive to ibuprofen as dogs are.[10] Gastrointestinal ulceration can occur in cats exposed to 4 mg/kg of carprofen; acute renal failure can develop at doses greater than 8 mg/kg (ASPCA APCC Database: Unpublished data, 2001-2005). Because of this sensitivity, most exposures require aggressive treatment.

Initial treatment should consist of gastric decontamination. If spontaneous vomiting has not begun and the ingestion was less than four hours earlier, induce emesis. Then administer activated charcoal and give repeated doses when exposure involves an NSAID that undergoes enterohepatic recirculation. To prevent gastrointestinal ulceration, administer an acid reducer such as an H_2 blocker (*e.g.* ranitidine or famotidine) or proton-pump inhibitor (*e.g.* omeprazole), as well as sucralfate and misoprostol (1 to 3 µg/kg orally b.i.d.)[12] for seven to 10 days. Monitor the cat for signs of gastrointestinal hemorrhage, such as melena or a decreased packed cell volume. Initiate fluid diuresis at twice the maintenance rate for at least 48 hours to prevent renal damage, and monitor the results of renal function tests.[11]

Acetaminophen

As with NSAIDs, acetaminophen is often administered to sick cats by their owners. Acetaminophen has a narrow margin of safety in cats. One adult tablet (325 to 500 mg) could be lethal. Clinical signs such as depression, vomiting, dyspnea, brown discoloration of the mucous membranes and blood due to methemoglobinemia, respiratory distress, swelling of the face and paws, and hepatic necrosis can develop at almost any level of exposure.[11] Signs of methemoglobinemia generally occur within hours of exposure, and liver damage may take a couple of days to manifest.

In asymptomatic cats, emesis may be initiated and activated charcoal administered. If methemoglobinemia is present, start oxygen therapy combined with a blood transfusion or polymerized bovine hemoglobin solution (Oxyglobin—Biopure) administration. Begin *N*-acetylcysteine (*e.g.* Mucomyst—Bristol-Myers Squibb) therapy immediately in any case of acetaminophen exposure in a cat. Dilute the *N*-acetylcysteine solution to a 5% concentration with 5% dextrose or sterile water; this will yield a 50-mg/ml solution. The loading dose is 140 mg/kg followed by 70 mg/kg every six hours for seven additional doses. Administer *N*-acetylcysteine orally unless either a bacteriostatic filter or a sterile solution of *N*-acetylcysteine (Acetadote—Cumberland Pharmaceuticals) is available. Adjunctive therapy includes intravenous fluids, cimetidine (to inhibit CP450 liver enzymes that activate acetaminophen to the toxic metabolite), and ascorbic acid, which may be used to help reduce methemoglobin to hemoglobin.[11] The prognosis in these cases is fair to guarded.

Anticoagulant Rodenticides

Although rodent baits are all similar in appearance, do not confuse anticoagulant rodenticides with bromethalin (a

neurotoxin) or cholecalciferol (a vitamin D analogue). Small doses of anticoagulants can cause coagulopathy by inhibiting the recycling of vitamin K_1 and blocking the synthesis of clotting factors II, VII, IX, and X. Clinical signs generally occur three to seven days after exposure when circulating clotting factors are depleted. Bleeding may occur in any location, so signs may be nonspecific and include weakness, lethargy, and dyspnea.[13] Hemorrhage is most common in the lungs, so cough or respiratory difficulty is a common finding.[14] Frank hemorrhage or ecchymoses may be seen. Lameness may occur if bleeding occurs in a joint, and various neurologic signs may be noted if bleeding occurs in the brain or spinal cord.[13]

Anticoagulant rodenticide poisoning can be diagnosed by measuring the prothrombin time (PT). PIVKA (proteins induced by vitamin K_1 absence or antagonism) and Thrombotest (Axis-Shield) time are other screening tests for anticoagulant toxicosis. PT and PIVKA tests are most sensitive to depletions of factor VII because it has the shortest half-life.[14] If performed within two to four hours of exposure, decontamination by inducing emesis and administering activated charcoal is effective at reducing the amount absorbed systemically. Otherwise, treatment with vitamin K_1 (3 to 5 mg/kg orally divided twice daily) is antidotal. Vitamin K_1 should be given for 14 days after warfarin exposure, for 21 days after bromadiolone exposure, and for 30 days after brodifacoum and all other anticoagulant exposure or unknown anticoagulant exposure.[14]

Also test the PT or PIVKA about 48 hours after cessation of vitamin K_1 treatment to determine whether the patient was treated long enough. If an animal presents in hemorrhagic crisis, treatment is generally supportive and should consist of whole blood or plasma transfusions and stabilization as needed as well as vitamin K_1.[13] If treatment is started before coagulopathy, the prognosis is excellent. The prognosis is guarded if the patient is already bleeding.

Amphetamines

In people, amphetamines in prescription medications are used for appetite suppression, attention deficit disorder, and narcolepsy. Another source of amphetamine exposure is illicit preparations of amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA), also known as *Ecstasy*. Amphetamines act as CNS stimulants by increasing catecholamine release, inhibiting catecholamine reuptake, and increasing release of serotonin.[15] Almost any exposure in a cat can result in clinical signs such as agitation, hyperthermia, tremors, seizures, tachycardia, hypertension, cardiac arrhythmias, and coma (ASPCA APCC Database: Unpublished data, 2002-2005).

Treatment should include gastric decontamination if the animal is asymptomatic, but a rapidity in the onset of clinical signs may limit the possibility for this. Monitor cardiovascular and CNS signs closely. Also monitor body temperature, and maintain it in a normal range. Administer acepromazine or chlorpromazine for agitation, and barbiturates may be used to control seizures.[16] Cyproheptadine may be used as a serotonin antagonist. Treat cardiac arrhythmias as needed (*e.g.* propranolol if tachycardia is present). Intravenous fluids will help promote elimination. Consider administering ammonium chloride or ascorbic acid to acidify the urine and promote elimination if acid-base balance can be monitored. The half-life of the drug and the duration of signs depend on the urinary pH,

and signs may be seen for 12 to 48 hours or more.[16] The prognosis with aggressive supportive care is good in most cases. VM

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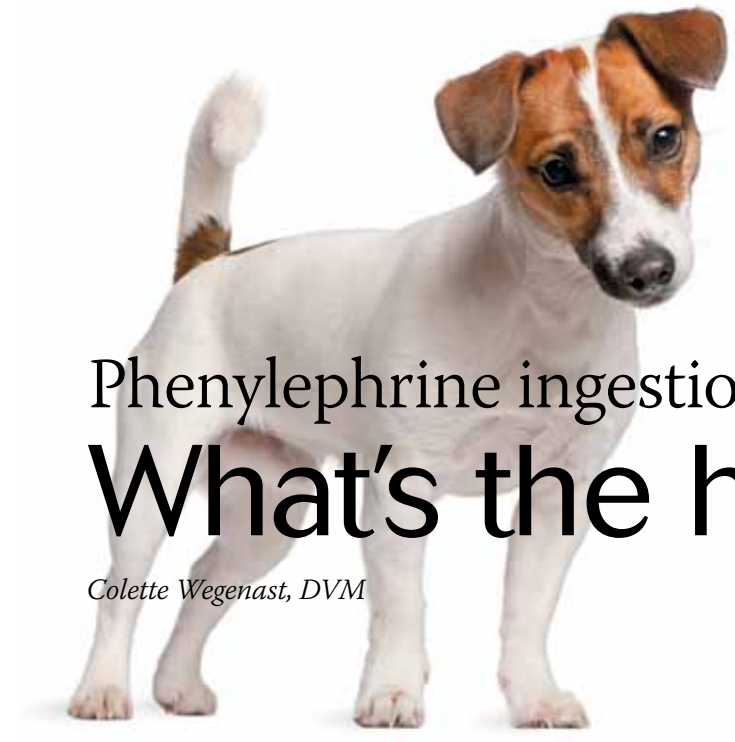

Phenylephrine ingestion in dogs
What's the harm?

Colette Wegenast, DVM

Phenylephrine is a sympathomimetic amine used orally in human medicine mainly as a decongestant. It is found in several over-the-counter cold remedies. Veterinary practitioners should be aware of its toxic potential in dogs since its use has likely increased as restrictions are placed on the sale of another common over-the-counter decongestant, pseudoephedrine, because of pseudoephedrine's involvement with methamphetamine production.

Exposure Risks For Dogs

As a decongestant, phenylephrine is available in nasal (0.25% to 1%) and oral formulations (5- to 10-mg tablets). The oral formulations are often combined with antihistamines, analgesics, expectorants, or antitussives. In an overdose, other ingredients present in the formulation such as acetaminophen or ibuprofen are often more concerning than the phenylephrine.

Parenteral formulations of phenylephrine are used to treat hypotension in animals and people. Phenylephrine is also used as an adjunct in spinal and local anesthesia.

Ocular preparations produce mydriasis and vasoconstriction. These formulations are used for intraocular examination and surgery and to differentiate conjunctival vascular injection from deep-episcleral injection. Ocular phenylephrine is also used in the diagnosis and treatment of glaucoma, treatment and prevention of synechiae, and diagnosis and classification of Horner's syndrome.[1,2]

Hemorrhoid creams, ointments, and suppositories also contain phenylephrine.

Toxicokinetics

Phenylephrine acts directly on alpha$_1$-adrenergic receptors. The stimulation of these receptors results in peripheral vasoconstriction and increased systolic and diastolic blood pressures. At high dosages, the stimulation of cardiac beta-adrenergic receptors may occur.[3] This can lead to cardiac stimulation.

After oral exposure, phenylephrine is extensively metabolized in the gastrointestinal tract and liver.[1,4] This high metabolization accounts for the low oral bioavailability of phenylephrine (38% in people).[1] It is primarily excreted in the kidneys in people.[1] Phenylephrine reaches a peak plasma concentration in 30 minutes.[5] The half-life is two to three hours. Adverse signs typically have a rapid onset and relatively short duration.[3]

Toxicity

The oral LD$_{50}$ of phenylephrine in rats

and mice is 350 mg/kg and 120 mg/kg, respectively.[6] Because of low oral bioavailability, the acute oral toxicity is lower for phenylephrine than with other sympathomimetics such as pseudoephedrine, and parenteral administration is more likely to result in marked clinical signs of toxicosis compared with oral exposure. An oral therapeutic dosage in dogs could not be located.

Clinical signs after overdose may include[2,3]:

- Gastrointestinal upset
- Hypertension
- Reflex bradycardia
- Central nervous system stimulation
- Lethargy
- Nervousness
- Agitation
- Tremors
- Seizures
- Cerebral hemorrhage
- Ventricular arrhythmias

APCC Data

The ASPCA Animal Poison Control Center (APCC) toxicology database was searched for oral phenylephrine exposures in dogs. Cases involving combinations of phenylephrine with other medications (*e.g.* analgesics, antihistamines, antitussives) and multiple agent exposures were excluded. Between January 1, 2007, and December 31, 2011, 178 dogs with clinical signs were identified. These dogs were considered to have a medium or high likelihood of suffering from phenylephrine toxicosis based on history of exposure and the clinical signs present. Of the 178 exposures, 89 were due to ingestion of hemorrhoid medications (creams, ointments, or suppositories), 80 were from ingesting tablets or capsules, and nine were due to ingestion of nasal drops and sprays.[7]

Hypertension is expected to be the main serious concern after phenylephrine overdose.

After ingestion of hemorrhoid preparations in 89 dogs, the most common signs were vomiting (75 dogs; 84%), lethargy (8 dogs; 9%), diarrhea (5 dogs; 6%), bradycardia (4 dogs; 4%), tachycardia (4 dogs; 4%), and trembling (4 dogs; 4%). In most cases, the dosages were unknown, so a range could not be determined. Hypertension was reported in two cases (2%). A systolic blood pressure of 170 mm Hg was reported at 11.9 mg/kg and a systolic blood pressure of 210 mm Hg was reported after an estimated dosage of 7 mg/kg.

In the nine dogs with clinical signs as a result of nasal spray or drop exposure, vomiting (9 dogs; 100%) and trembling (1 dog; 1%) were the only signs reported.[7]

The most common signs after tablet or capsule ingestion in 80 dogs were vomiting (63 dogs; 79%), hyperactivity (9 dogs; 11%), lethargy (7 dogs; 9%), panting (6 dogs; 8%), and trembling (4 dogs; 5%). Dosages ranged from 0.23 to 30 mg/kg. Hypertension was not reported.[7]

The ASPCA APCC data are consistent with the expected low oral toxicity of phenylephrine, probably due to phenylephrine's low bioavailability. Based on phenylephrine's physiologic effects, hypertension is expected to be the main serious concern after phenylephrine overdose. However, hypertension was noted in only 2% of cases and only after exposures to hemorrhoid medications. This may possibly be due to oral mucosal absorption of phenylephrine from the creams, ointments, and suppository formulations. One of the hypertensive dogs made a full recovery within five hours. The outcome for the other dog was not known.[7]

Treatment

An exact dosage of concern in dogs after oral exposure is unknown. Because of phenyleph-

rine's low bioavailability, severe signs after oral exposure are unlikely. If needed, emesis with 3% hydrogen peroxide (2.2 ml/kg orally—maximum of 45 ml—repeat once in 15 minutes if not successful) or apomorphine (0.03 mg/kg intravenously or into the conjunctival sac) could be considered if the exposure is recent and the patient is not exhibiting clinical signs.[8,9] Consider the risk for aspiration if inducing emesis after ingestion of ointments. Activated charcoal is not typically necessary. Monitor dogs for gastrointestinal upset, hyperactivity, lethargy, and, potentially, hypertension (especially after ingestion of creams, ointments, or suppositories containing phenylephrine).

Acepromazine (0.02 mg/kg intravenously) can be used to control the stimulatory signs and mild hypertension.[10] Nitroprusside (1 to 2 µg/kg/minute) may be necessary if marked hypertension persists.[11] Intravenous fluids can be used for supportive care. The gastrointestinal signs are often self-limiting but should respond to symptomatic care if necessary.

Monitoring

In dogs exhibiting marked clinical signs, monitor blood pressure, heart rate and rhythm, temperature, and central nervous system status. Also, monitor for gastrointestinal upset. A baseline complete blood count and serum chemistry profile may be performed in patients exhibiting marked central nervous system or cardiovascular effects, although no direct specific laboratory changes are expected.

Summary

Phenylephrine is a sympathomimetic alpha$_1$-adrenergic agonist commonly found alone or in combination as a decongestant and as the active ingredient in hemorrhoid preparations. Because of its low oral bioavailability, phenylephrine has a wider safety margin than does pseudoephedrine (another common sympathomimetic decongestant). Per ASPCA APCC experience, the most common signs in dogs after ingestion are vomiting, hyperactivity, and lethargy. However, there is a risk for more serious sequelae such as hypertension, heart rate changes, and central nervous system stimulation. VM

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Managing acute carprofen toxicosis in dogs and cats

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Carprofen, a nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid class, is commonly used in small-animal practice for its analgesic, anti-inflammatory, and antipyretic properties. Its main uses in dogs are to treat pain and inflammation associated with osteoarthritis and control postoperative pain associated with soft tissue and orthopedic surgeries. More than 10 million dogs have been treated to date.[1]

Available as an injectable solution (50 mg/ml) and 25-, 75-, and 100-mg caplets and chewable tablets, Rimadyl (Pfizer Animal Health) is labeled in the United States for dogs only. The manufacturer's recommended dosage is 2 mg/lb (4.4 mg/kg) orally or subcutaneously daily (alternatively, 1 mg/lb [2.2 mg/kg] b.i.d.), and the injectable product is recommended to be given two hours before surgery to manage postoperative pain. Intramuscular and intravenous routes are extralabel and have also been reported.[2] Generic formulations of carprofen—Vetprofen (Vétoquinol), Novox (Vedco), and Carprofen Caplets (Putney)—are also available as 25-, 75-, and 100-mg caplets for dogs only.[3]

The ASPCA Animal Poison Control Center (APCC) has received many calls regarding carprofen exposures in dogs and cats over the years (ASPCA APCC Database: Unpublished data, 2001-2009). This report details public cases in the computerized database (November 1, 2001 through April 27, 2009) that fulfill the following criteria in dogs and cats:

1. Single agent exposures
2. Observed exposures or those cases documented by evidence such as a chewed bottle
3. Clinical cases assessed by ASPCA APCC veterinarians as likely related to the agent
4. Acute overdoses only in dogs (to exclude idiosyncratic hepatic reactions)
5. Oral products only

Therapeutic Mechanism Of Action

Like most NSAIDs, carprofen is thought to mediate its beneficial therapeutic effects by inhibiting the enzyme cyclooxygenase (COX), which catalyzes the cyclization and oxygenation of arachidonic acid to prostaglandins. Discovered in 1991, COX-2 is the isoform of the enzyme induced by proinflammatory cytokines and mitogens,[4] and COX-2 inhibition is the main intended target for the

therapeutic effects of NSAIDs, particularly the more recently approved drugs. A higher ratio of COX-2 to COX-1 inhibition is associated with greater therapeutic efficacy and fewer adverse effects. However, in animals with underlying gastrointestinal disease or in those receiving concurrent NSAID or glucocorticoid therapy, any amount of COX-1 inhibition could be detrimental. Preexisting gastrointestinal inflammation, overdosage, and close temporal use of other NSAIDs or glucocorticoids in dogs receiving a selective COX-2 inhibitor (deracoxib) have resulted in gut perforation and death.[5] The literature reports variable selectivity of COX-2 vs. COX-1 inhibition by carprofen.[4,6-12]

Toxic Mechanism Of Action

COX-1, the constitutive and cytoprotective isozyme, has many beneficial roles in the body. In the stomach, COX-1 reduces gastric acid secretion by parietal cells, maintains gastric mucosal blood flow mediated by vasodilation, and stimulates mucus and bicarbonate production by epithelial cells.[13] Inhibiting this

Risk factors for carprofen toxicosis

A variety of risk factors exist for carprofen toxicosis. Animals with any previous reaction to the drug are at risk. Aged animals may have documented compromise of the liver or kidneys or subclinical disease that becomes clinical with the toxicosis.[1]

Any condition that results in dehydration can reduce blood flow to the kidneys and exacerbate the potential for acute renal failure, decreasing the dosage of concern for renal toxicosis to as little as 30 mg/kg (ASPCA APCC Database: Unpublished data, 2001-2009). Examples include patients with congestive heart failure receiving diuretic therapy or those with reduced cardiac output regardless of medical therapy. Unreplaced fluids lost through vomiting or diarrhea with carprofen toxicosis or underlying gastrointestinal disease may hasten the onset of renal damage.

Because the liver and kidneys are responsible for carprofen's metabolism and clearance, any preexisting disease involving these organs is likely to amplify the toxic risk by increasing the half-life and plasma drug concentration.[2]

Concurrent administration of drugs that are also highly protein-bound may result in worsening carprofen toxicosis or create an additional toxicosis with the second agent. Some examples include phenytoin, valproic acid, oral anticoagulants, other NSAIDs, glucocorticoids, salicylates, sulfonamides, sulfonylureas, methotrexate, and digoxin.[2,3]

Because of the potential for changes in platelet function and coagulopathies associated with fulminant liver failure, animals with underlying coagulation disorders such as von Willebrand's disease may be at increased risk for carprofen toxicosis. The manufacturer has not specifically tested the drug in these patients but warns against its use in those animals.[1]

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Table 1

Clinical Signs Associated with Acute Carprofen Toxicosis in Dogs*

Clinical Sign	Number of Cases
Gastrointestinal	
Vomiting (bloody)	456 (30)
Diarrhea (bloody)	46 (15)
Anorexia	53
Melena/dark or black feces	11
Tense or painful abdomen	10
Energy Level and Mentation	
Lethargy/depression/weakness	94
Hyperactivity/restlessness	3
Coma/stupor	2
Hepatic	
Elevated ALT	40
Icterus/icteric serum/elevated bilirubin	14
Ascites	1
Renal	
Azotemia	55
Dehydration	13
Hematuria/discolored urine/hemoglobinuria	8
Polydipsia	8
Acute renal failure	3
Oliguria	2
Proteinuria	2
Urinary tract infection	2
Urinary casts	1
Neurologic	
Tremors	7
Ataxia	5
Seizures	3

***Total number of 584 cases of toxicosis; dose range = 3.94 to 1,984 mg/kg. Death was reported in three dogs.**

isozyme with NSAID therapy can result in gastrointestinal ulceration, hemorrhage, and gut perforation with septic peritonitis as a sequela. Direct damage to the gastric mucosal microcirculation and the formation of capillary microthrombi can also occur with NSAID use.[13]

In the kidneys, COX-1 activation results in prostaglandin I, E, and D production,[14] which dilates renal vascular beds and diminishes vascular resistance, resulting in enhanced organ perfusion. Inhibition of these beneficial prostaglandins results in decreased renal blood flow, ischemia of the medullary papillae, and papillary necrosis.[14]

In platelets, COX-1 converts arachidonic acid to thromboxane A_2, which is proaggregatory and vasoconstrictive. Its inhibition can be beneficial in preventing myocardial infarction in people[3] and has been associated with subclinical increased bleeding times, decreased platelet aggregation, and decreased clot strength in dogs treated with a variety of NSAIDs.[15,16]

At therapeutic dosages, carprofen has greater selectivity for COX-2 vs. COX-1. Overdoses have been shown to increase COX-1 inhibition[4] and the likelihood of adverse effects.

A subset of dogs treated with therapeutic doses of carprofen has exhibited an idiosyncratic hepatocellular toxicosis. A mean

onset of clinical signs in dogs about 20 days after the start of therapy has been reported.[17] Discontinuing the drug and administering supportive care resulted in complete recovery in most of the dogs in that report. This syndrome has not been reported in cats.

Because of the distinct pathologic mechanisms of idiosyncratic hepatocellular toxicosis vs. those of acute carprofen toxicosis, we will not discuss idiosyncratic hepatocellular toxicosis further. However, we will address hepatocellular injury due to intrinsic, dose-related effects associated with acute carprofen overdoses. The manufacturer reports about a 20-IU increase in alanine aminotransferase activity at doses 5.7 times the therapeutic dose in separate safety studies in dogs given carprofen orally for 13 weeks and one year[12] and hypoalbuminemia in two of eight dogs treated at 10 times the therapeutic dose for 14 days.[12]

Pharmacokinetics

Pharmacokinetics plays an important role in carprofen toxicosis. Nearly 90% to 100% of the ingested drug is bioavailable,[18] with a peak plasma concentration in one to three hours.[2,19] Carprofen is also highly protein-bound, which can exacerbate the toxic effects of coadministered drugs that are also highly protein-bound, particularly drugs with a narrow margin of safety (*e.g.* anticoagulants, digoxin, methotrexate) as well as in dogs in which hepatic function may be abnormal.[2,13] In dogs, the elimination half-life ranges from eight to 18 hours[2,4,19]; 70% to 80% of carprofen is metabolized by direct conjugation to an ester glucuronide followed by oxidation to phenol and further conjugation. These conjugated phenols are eliminated in the feces. Smaller amounts of carprofen are excreted as hydroxy metabolites in urine.[2,20] Enterohepatic circulation has been documented for carprofen.[19]

Because of cats' limited ability to metabolize carprofen via glucuronidation, the drug's elimination half-life (20.1 ± 16.6 hours)[21] in that species is longer than in dogs. Consequently, use of the drug in cats poses a far greater risk of adverse effects. In the United States, carprofen use in cats remains extralabel, so the pharmacokinetic differences in this species should be kept in mind, and extreme caution should be exercised when administering carprofen in cats.

Acute Overdosage

Because of dogs' relative lack of dietary discretion and the palatability of chewable Rimadyl tablets, it is not unusual for a dog to ingest an entire bottle of carprofen tablets if it is accessible (ASPCA APCC Database: Unpublished data, 2001-2009). With a maximum of 240 caplets per bottle and 100 mg per tablet,[3] extreme ingestions are possible. And given the narrow margin of safety in cats, ingesting just one 25-mg tablet is potentially serious.

Table 1 lists the clinical signs reported by the ASPCA APCC in cases of acute overdoses in dogs. Vomiting is the most common finding, seen in 78% of cases, with an array of additional signs affecting the gastrointestinal system predominating thereafter. Fewer patients exhibit hepatic, renal, or neurologic signs or hematologic abnormalities. Nonspecific changes in energy status or mentation, such as lethargy or depression, are not uncommon.

Table 2 lists the comparable statistics for carprofen toxicoses in cats. With far fewer cases because of the relative dietary discretion of cats, the same array of signs can be seen with feline toxic ingestions.

In otherwise healthy dogs, a review of the ASPCA APCC database historically indicated that fairly severe gastrointestinal signs may be seen at doses exceeding 20 mg/kg and that diuresis to prevent renal damage should be recommended at 40 mg/kg and above (ASPCA APCC Database: Unpublished data, 2001-2009).

Hepatic damage may occur with any dose, but the potential

Table 2

Clinical Signs Associated with Acute Carprofen Toxicosis in Cats*

Clinical Sign	Number of Cases
Vomiting (bloody)	54 (4)
Depression/lethargy/listless	19
Azotemia	16
Anorexia	15
Dehydration	6
Hyperphosphatemia	5
Acute renal failure	4
Diarrhea	4
Elevated ALT	4
Hyperkalemia	3
Hypoalbuminemia	3
Hypersalivation	2
Oral ulcers	2
Pale mucous membranes	2
Abdominal pain	2
Leukocytosis	2
Hypersalivation	2

***Total number of 76 cases of toxicosis; dose range 2.9 to 793 mg/kg. Death was reported in four cats.**

for nonidiosyncratic damage, by definition, should worsen with increased doses. According to the ASPCA APCC database, mild, transient, and often subclinical elevations of alanine transaminase (ALT) and alkaline phosphatase (ALP) activities have been seen with single, acute exposures beginning in the 40-mg/kg range in dogs.

With single, acute exposures exceeding 100 mg/kg in dogs, more moderate to severe elevations in ALT and ALP activities can be seen, and these are often associated with clinical illness. Prophylactic administration of s-adenosylmethionine (SAMe) (17 to 20 mg/kg or more per day on an empty stomach) is recommended in dogs at greater risk for hepatic damage. A similar trend has not been identified in cats, but prophylactic SAMe administration (200 mg/kg on an empty stomach) should be considered in cats as well.

Neurologic signs, including seizures, stupor, and coma, tend to be seen with extreme ingestions. Respectively, these signs have been seen in ASPCA APCC cases in carprofen ingestions of 281, 536, and 645 mg/kg in dogs. Death despite treatment has been reported at 536 mg/kg. Definitive damage to the kidneys, as evidenced by the presence of urinary casts, was seen in a dog that ingested 48 mg/kg of carprofen.

In cats, the ASPCA APCC data indicate that ingestions of 4 mg/kg and above would be expected to cause more than mild gastrointestinal signs, and ingestions of 8 mg/kg and above may result in acute renal failure (ASPCA APCC Database: Unpublished data, 2001-2009). One 3-month-old kitten received 8.6 mg/kg of carprofen orally and was euthanized after acute renal failure developed. The lowest reported dose for death in a cat was ingestion of a possible range of 27.5 to 45.8 mg/kg (ASPCA APCC Database: Unpublished data, 2001-2009).

For both dogs and cats, keep in mind this information is from cases in which medical intervention had been sought

and may not reflect the lowest doses at which signs may arise in untreated animals. Furthermore, because complete clinical findings and case outcomes are not always reported to the ASPCA APCC and because not all dosages are represented in the exposures reported, the lowest reported dosage at which a specific adverse effect has been seen may not be the true lowest dosage at which that effect is possible.

Pretreatment Diagnostic Tests

Ideally, any animal with acute carprofen exposure expected to result in moderate or severe clinical signs should undergo pretreatment baseline diagnostic tests to better assess the patient's risk and to tailor the treatment. This assessment is especially true for carprofen exposure because a variety of underlying illnesses may complicate the toxicosis (see the boxed text titled "Risk factors for carprofen toxicosis"). A complete blood count to obtain a baseline packed cell volume; a serum chemistry profile to assess blood urea nitrogen (BUN), creatinine, and electrolyte concentrations as well as liver enzyme activities; and a urinalysis to evaluate the urine specific gravity would be ideal.

Treatment

Treatment involves instituting decontamination, protecting the gastrointestinal tract and kidneys, providing supportive care, and monitoring gastrointestinal, renal, and hepatic function.

Decontamination

If the exposure history indicates a potential for adverse effects, decontamination is warranted. If a patient presents within a couple of hours of ingesting an overdose of carprofen and has no condition that precludes it, induce emesis. In dogs, administer 2.2 ml/kg of 3% hydrogen peroxide (maximum 45 ml) orally. You may repeat this dose if the patient fails to vomit within 15 minutes (ASPCA APCC Database: Unpublished data, 2001-2009). Alternatively, apomorphine can be given intravenously (0.04 mg/kg), subcutaneously (0.08 mg/kg), or in the conjunctival sac (0.25 mg/kg).[2] Examining the vomitus often does not allow quantification of recovered medication because the residue of the chewable Rimadyl is often indistinguishable from partially digested food. Nevertheless, it is advisable to attempt to reevaluate the exposure by examining the vomitus.

Inducing emesis is an unpredictable endeavor in cats. The response to hydrogen peroxide is typically poor; apomorphine can stimulate the central nervous system, and xylazine (0.44 mg/kg intramuscularly) can cause central nervous system depression and increase the risk of aspiration.[2] Decontamination with activated charcoal (*e.g.* ToxiBan—Vet-a-Mix) may be the best first step in cats.

Even in extreme overdose cases, the prognosis is often excellent.

After emesis has stopped, orally administer the first dose of activated charcoal. The ToxiBan label recommends 10 to 20 ml/kg for a small animal.[22] Because of concerns for hypernatremia, however, the ASPCA APCC recommends a lower dose of 6.6 to 11 ml/kg of the 10% solution (alternatively, 1 to 2 g/kg of the 100% granules). A formulation containing a cathartic such as sorbitol is recommended for the first dose.

An experimental study in beagles involving an overdose of 16 mg/kg carprofen given orally documented the efficacy of administering 2.5 g/kg activated charcoal 30 minutes after exposure. The plasma carprofen concentration was significantly reduced with activated charcoal administration relative to the control group.[23] Because of carprofen's enterohepatic circulation, multiple doses of activated

Table 3

GI Protectants and Antiemetics Used in Dogs and Cats with Carprofen Toxicosis

Drug	Dosage in Dogs	Dosage in Cats	Route
Gastrointestinal Protectants			
Misoprostol	1-5 µg/kg t.i.d.	Not recommended	PO
Famotidine	0.5 mg/kg once or twice a day	0.5 mg/kg once or twice a day	PO, IM, IV, SC
Omeprazole	0.5–1 mg/kg once a day (maximum of 20 mg)	0.7–1.5 mg/kg once or twice a day*	PO
Sucralfate	< 40 lb: 0.5 g t.i.d. > 40 lb: 1 g t.i.d.	0.25–0.5 g b.i.d. to t.i.d.	PO
Antiemetics			
Metoclopramide	0.1–0.4 mg/kg q.i.d. or 1–2 mg/kg/day constant-rate infusion	0.2–0.4 mg/kg t.i.d. to q.i.d. or 1–2 mg/kg/day constant-rate infusion	PO, SC IV, constant-rate infusion
Ondansetron	0.1–1 mg/kg once to twice daily or (0.11–0.176 mg/kg b.i.d. to q.i.d.)	0.22 mg/kg b.i.d. to t.i.d. or (0.1–0.15 mg/kg b.i.d. to q.i.d.)	PO (IV)
Chlorpromazine	0.5 mg/kg t.i.d. to q.i.d.	0.5 mg/kg t.i.d. to q.i.d.	IV, IM, SC
Maropitant	1 mg/kg once a day	1 mg/kg once a day (extralabel)	SC

Not recommended in cats per Talcott PA. Nonsteroidal antiinflammatories. In: Peterson ME, Talcott PA, eds. *Small animal toxicology*. 2nd ed. St. Louis, Mo: Elsevier/Saunders, 2006;902-933.

charcoal can be beneficial. Subsequent doses without cathartic are given every eight hours and at a reduced dose (3.3 to 5.5 ml/kg of the 10% solution) to minimize the potential for osmotic diarrhea and hypernatremia. To further minimize the potential for these adverse effects, the number of doses of activated charcoal is typically limited to three, even with the most extreme overdoses.[24]

Gastrointestinal protection

Aggressive administration of gastrointestinal mucosa protectants (*Table 3*) is warranted as a precaution for seven to 10 days after exposure to carprofen overdoses (ASPCA APCC Database: Unpublished data, 2001-2009). The prostaglandin E_1 analogue, misoprostol, is recommended for dogs, especially if the carprofen dose exceeds 20 mg/kg or the patient is exhibiting signs consistent with ulceration. Misoprostol is available in 100- and 200-µg tablets. Side effects include diarrhea, abdominal pain, vomiting, and flatulence, which may be confused with the underlying carprofen toxicosis. Because of the potential for adverse effects after several days of use, the veterinarians at the ASPCA APCC limit misoprostol administration to three to five days after exposure (ASPCA APCC Database: Unpublished data 2001-2009). Misoprostol is also used as an abortifacient, so its use is not recommended in pregnant dogs. Veterinary personnel or pet owners who may be concerned with this potential should wear gloves when administering the drug or avoid

handling it altogether.[2]

Additionally, gastric acid production can be decreased with an H_2 antagonist, such as famotidine, or the proton pump inhibitor omeprazole.

A third measure to minimize the potential for ulcerative effects is to administer sucralfate, which reacts with hydrochloric acid in the stomach to form a protective paste at the site of ulceration.[2] Sucralfate administration is recommended 30 minutes before an H_2 antagonist or proton pump inhibitor since it requires an acidic environment to be efficacious.[2]

Prevent Renal Necrosis

To prevent renal papillary necrosis with carprofen overdoses, crystalloid fluid administration at twice the maintenance fluid rate (60 ml/lb/day) is indicated for 48 hours after exposure in dogs to promote diuresis. Carprofen's longer and more variable half-life in cats may necessitate diuresis for 72 hours. The choice of crystalloid should be dictated by a patient's electrolyte and acid-base status. If BUN and creatinine concentrations (see "Additional monitoring" below) are normal at 48 hours, the fluids may be tapered over 24 hours and then the renal values reevaluated at 72 hours. Monitor urine output throughout the diuresis period to ensure that the patient is not oliguric or anuric. Renal damage has been documented in one case as early as 24 hours after carprofen exposure by the presence of granular casts in the urine (ASPCA APCC Database: Unpublished data, 2001-2009).

Additional Symptomatic Treatment

Antiemetics are indicated in actively vomiting patients (*Table 3*). If an animal is critically anemic, a whole blood transfusion is warranted. Severe hypoproteinemia or coagulopathy can be treated with a plasma transfusion (10 to 30 ml/kg intravenously).[25] Vitamin K_1 may be administered in patients with fulminant liver failure and coagulopathies.[26] Diazepam may be given as needed for seizures. Pain due to gastrointestinal ulceration should be treated with opioid analgesia. Diuretics and dopamine may be necessary to restore urine production in oliguric or anuric animals. Hemodialysis[27] or peritoneal dialysis may be an option in patients with acute renal failure if finances are not limited. A more thorough discussion of acute renal failure treatment is presented elsewhere.[28-30] Hepatoprotective agents, such as S-adenosylmethionine (SAMe) or silymarin, can be administered in stable patients long-term until liver enzyme activities reveal no further hepatocellular damage. Broad-spectrum antibiotics are indicated if ulceration or hepatic compromise is present.

Additional Monitoring

In patients hospitalized for diuresis, daily assessment of BUN and creatinine concentrations, packed cell volume, liver enzyme activities, and urine output and character (*e.g.* presence of casts, urine protein:creatinine ratio) and frequent monitoring of hydration status are indicated. Normal test results related to renal and hepatic function 72 hours after carprofen exposure are not anticipated to elevate thereafter. Pain due to gastric ulceration may not become clinically evident until the analgesic effect of carprofen has worn off, so monitor patients for several days thereafter for melena, anorexia, lethargy, and abdominal pain.

Prognosis

If perforating or bleeding ulcers develop to the point of peritonitis or severe anemia, respectively, the prognosis understandably worsens. Severe azotemia, oliguria, anuria, and coagulopathy secondary to acute hepatic failure also carry a poorer prognosis. Even in extreme overdose cases, however, the prognosis with acute carprofen toxicosis is often excellent with prompt decontamination, diuresis, and gastrointestinal supportive care. VM

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Mushroom poisoning in dogs

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Mushroom poisoning of companion animals, particularly dogs, is a potentially underestimated problem in North America. Because of their wandering and scavenging nature, dogs seem particularly prone to mushroom poisoning.[1-8] While there have been sporadic reports of mushroom poisoning in dogs in the veterinary literature, [1-8] anecdotal experience in the Pacific Northwest suggests it is more prevalent than the literature indicates.

This article summarizes the clinical effects of the toxicologically important mushrooms in North America. Spring, summer, and fall are the principal seasons for mushroom poisoning in most of North America.[9]

Identification and treatment

Toxic mushrooms are divisible into eight groups based on their toxin type (*Table 1*).[9] Six of these groups are of potential veterinary significance, and representative members of these groups are common throughout North America.[9] In line with the adage "There are old mushroom hunters, there are bold mushroom hunters, but there are no old, bold mushroom hunters," all wild-growing mushrooms should be regarded as toxic until proven otherwise.

Ideally, samples of the ingested mushrooms should be brought into the clinic along with the affected animal. Do not place mushrooms for identification in a plastic bag; instead, wrap them in a moist paper towel or wax paper or place them in a paper bag. Identifying mushroom species is often complex, so consult a human poison information center with experience in mushroom identification (*e.g.* the Oregon Poison Center [(800) 222-1222]) or a mycologist as needed.[9,10]

Cyclopeptides

Amanita, Galerina, and *Lepiota*

1. *Amanita phalloides*, the death cap mushroom, is the most common cause of potentially fatal mushroom poisoning in people and dogs.

Table 1

Toxicologic Classification of Toxic Mushrooms

Toxin Type	Relevant Species	Methods of Toxicity
Cyclopeptides	*Amanita* species (death caps, death angels, destroying angels, deadly agaric), *Galerina* species	Amatoxins inhibit RNA and DNA transcription, affecting cells with the highest replication rates. Phallotoxins irreversibly polymerize hepatic actin filaments, resulting in cholestasis.
Monomethylhydrazine	*Gyromitra* species (false morels)	Gyromitrin is converted to monomethylhydrazine. Other toxic hydrazines are also present. They antagonize pyridoxine (vitamin B_6), an essential cofactor for the synthesis of GABA. They also directly inhibit the synthesis of GABA.
Coprine	Coprinus atramentarius (ink cap)	Hyperacetaldehydemia is triggered if ethanol (alcohol) is consumed within two to 72 hours after consuming the mushrooms. Probably not of veterinary significance.
Muscarine	*Inocybe, Clitocybe, Panaeolus, Gymnopilus, Boletus, Hebeloma, Mycena, and Omphalotus* species	Produces the classical muscarinic cholinergic clinical signs: SLUD (salivation, lacrimation, urination, and diarrhea).
Isoxazole derivatives	*Amanita* species	Ibotenic acid and muscimol are psychoactive and generally produce distortions in visual perception.
Psilocybin and psilocin	*Psilocybe, Panaeolus, Copelandia, Gymnopilus, Pluteus*, and *Conocybe* species (hallucinogenic or magic mushrooms)	The LSD-like compounds cause dysphoria, hallucinations, and sympathomimetic effects.
GI irritants	*Agaricus, Boletus, Chlorophyllum, Entoloma, Gomphus, Hebeloma, Lactarius, Naematoloma, Omphalotus, Paxillus, Ramaria, Rhodophyllus, Russula, Scleroderma, and Tricholoma* species	Most of the agents that trigger acute GI distress have not been identified. Idiosyncratic and allergic mechanisms have been proposed. Many, but not all, of these toxins are inactivated by cooking.
Orelline and orellanine	*Cortinarius* species from Europe and Japan	These species cause irreversible acute renal failure; often the only effective treatment is renal transplant.

species musrooms contain toxic cyclopeptides. *Amanita* species are the most commonly documented cause of fatal mushroom poisoning in dogs,[1,2,4-8] and they account for 95% of mushroom-related fatalities in people.[9] *Amnita phalloides*, the death cap mushroom (*Figure 1*), accounts for more than 50% of all mushroom-associated deaths in people and most of the reported fatal cases in dogs.[1,2,6,9]

The toxic cyclopeptides in these mushrooms are amatoxins, phallotoxins, and virotoxins.[8,9] These peptides are rapidly absorbed from the gut, and their duration of action is increased by enterohepatic circulation and active resorption of amatoxins from the renal glomerular filtrate. Amatoxins and phallotoxins are responsible for most of the pathologic effects.[9] Amatoxins interfere with DNA and RNA transcription and, thus, selectively affect the rapidly replicating cells of the gastrointestinal (GI) and renal tubular epithelium and liver. Phallotoxins irreveribly polymerize hepatic actin filaments, triggering hepatic cholestasis.[9]

Typically, 10 to 12 hours pass between consumption and the onset of clinical signs.[9] This delay is an important differential diagnostic feature of cyclopeptide ingestion and is probably due to the time required for amatoxins to bind to intranuclear RNA polymerase II.[9]

There are three distinct sequential phases of cyclopeptide poisoning. The initial gastroenteritis phase is characterized by profuse bloody diarrhea, vomiting, nausea, abdominal pain, dehydration, electrolyte imbalance, fever, tachycardia, and hyperglycemia.[9] This phase typically lasts about 24 hours. The resolution of clinical signs and subclinical elevations of serum alanine transaminase and aspartate transaminase activities characterize the onset of the 12- to 24-hour latent phase.[9] The final—and often terminal—hepatorenal phase of poisoning begins three to four days after ingestion.[9] Severe hepatic dysfunction, severe renal failure, cerebral edema, icterus, elevated serum hepatic enzyme activities, hypoglycemia, coagulopathies and hemorrhage, azotemia, metabolic acidosis, and sepsis characterize the hepatorenal phase. In addition, neurologic dysfunction including hepatic encephalopathy and coma can occur.[9] Typically, the animal dies three to seven days after ingestion.[9]

The final hepatorenal phase of cyclopeptide poisoning begins three to four days after ingestion.

Treatment. Early aggressive decontamination and enhanced elimination are critical.[6,8,9] Performing emergency upper GI decontamination (inducing emesis or gastric lavage) is probably not beneficial more than four hours after ingestion since phallotoxins and amatoxins are rapidly absorbed from the GI tract and do not form gastric concretions or delay gastric emptying.[9] Induce emesis only in asymptomatic animals because of the risks associated with this procedure.

The effectiveness of activated charcoal is unknown, but its use has been recommended.[9] Administer an activated charcoal slurry (1 g/5 ml water) orally at a dose of 2 to 5 ml/kg in combination with a mild cathartic (sorbitol 3 mg/kg orally).[11] Repeated doses of activated charcoal may be administered every four to six hours in an attempt to reduce the enterohepatic circulation of amatoxins and may be of value up to 48 hours after ingestion.[9] Adequately hydrate patients treated with multiple doses of activated charcoal to prevent constipation.[11] Repeated doses of sorbitol may cause marked hypotension or hypovolemic shock, particularly in patients with underlying

cardiovascular problems or in small patients, so monitoring is required if repeated doses of activated charcoal and sorbitol are administered.[11]

Enhanced elimination using peritoneal dialysis and other methods of extracorporeal elimination has yielded occasional therapeutic successes in people.[6,9] Administering parenteral penicillin G benzathine at doses greater than 4,300 U/kg, which displaces amatoxins from plasma protein-binding sites making them more available for renal excretion, has been claimed to improve survival in people.[9] However, a recent 20-year retrospective analysis has demonstrated that this treatment, alone or in combination with other agents has little efficacy.[12]

Supportive care involves administering intravenous crystalloids, glucose, fresh frozen plasma, GI protectants (*e.g.* kaolin/pectin 1 to 2 ml/kg orally every six to 12 hours), and broad-spectrum parenteral antibiotics to reduce the risk of sepsis. Oral supplementation or parenteral treatment with vitamin K_1 (2.5 to 5 mg/kg daily) and packed red blood cell or whole blood transfusions may be required if bleeding is severe.

Silibinin dihydrogen disuccinate disodium and acetylcysteine have been suggested as antidotes for cyclopeptide poisoning.[9] Silibinin is a semisynthetic, commercialized, active derivative of silymarin, the hepatoprotectant and antioxidant mixture of medicinal flavonolignans derived from milk thistle (*Silybum marianum*). Administering silibinin intravenously (20 to 50 mg/kg/day in four doses) substantially increases the survival rate in people.[9] Unfortunately, the injectable form of this antidote is not available in the United States, and the poor water solubility and bioavailability of silymarin may limit the effectiveness of this potential antidote when orally administered. Silipide, a complex of silymarin and phosphatidylcholine (lecithin), is about 10 times more bioavailable than silymarin, but its effectiveness as an oral antidote for *A. phalloides* mushroom poisoning has not been investigated. The effectiveness of acetylcysteine for treating mushroom cyclopeptide poisoning is questionable. However, given its low risk of adverse effects, treatment can be attempted by administering a loading dose of 140 mg/kg orally followed by 70 mg/kg orally every six hours for as long as the patient needs it based on clinical judgment.

Monomethylhydrazine

Gyromitra species of mushrooms, often called *false morels*, vary considerably in their toxicity from year to year and location to location. Of the several different toxic hydrazine compounds found in these mushrooms, gyromitrin is the best known.[9] The hydrolysis of gyromitrin in the gut results in the formation of monomethylhydrazine, a GI irritant, and subsequent gastroenteritis within six to eight hours of ingestion. Most cases are relatively mild and self-limiting; however, extreme poisonings characterized by hepatic damage have been reported in people.[9] Monomethylhydrazine also directly inhibits the synthesis of gamma-aminobutyric acid (GABA) within the central nervous system (CNS) and antagonizes pyridoxine (vitamin B_6), an essential cofactor for the synthesis of GABA. The net result is uncontrolled CNS electrical activity, anxiety, restlessness, excitation, and seizures.[9]

Treatment. Pyridoxine (25 mg/kg administered as a slow intravenous infusion over 15 to 30 minutes) has been recommended as an antidote for the neurologic effects of this type of mushroom poisoning.[9] Additional treatment consists of upper GI decontamination and supportive care. Because of the risk of precipitating seizures, inducing emesis in severe monomethylhydrazine poisoning cases is potentially risky. Inducing emesis with due clinical prudence and judgment may be appropriate for milder cases.

Activated charcoal administration has been recommended, although its effectiveness is unknown.[9] Rehydration by using intravenous crystalloids is the most commonly required supportive treatment.[9] Oral GI protectants may be beneficial. If necessary, anxiety, restlessness, and seizures can be controlled with a benzodiazepine (0.25 to 0.5 mg/kg diazepam intravenously or intramuscularly).[9]

Coprine

Coprine, the major fungal toxin associated with *Coprinus atramentarius* mushroom poisoning, inhibits aldehyde dehydrogenase, thus inhibiting the conversion of ethanol (alcohol) to acetate and resulting in an accumulation of acetaldehyde. This effect only occurs if there is an association between the consumption of C. *atramentarius* mushrooms and ethanol.[9] If ethanol is not consumed concurrently with these mushrooms, the poisoning does not occur. Thus, this poisoning is unlikely in veterinary medicine.

Muscarine

Muscarine is a muscarinic receptor agonist that produces postganglionic parasympathomimetic effects, such as increased genitourinary muscle tone, bradycardia, miosis, and salivation.[9] The most common mushrooms involved in muscarine poisoning include members of the *Inocybe* and *Clitocybe* genera.[9] Although *Amanita muscaria* has been classically associated with muscarine toxicity, it contains insignificant amounts of this toxin.[9] Clinical signs usually occur within two hours after ingestion and are characterized by the acronym *SLUD* (salivation, lacrimation, urination, diarrhea).[9] Other common clinical signs include bradycardia, hypotension, shock, dyspnea and wheezing due to bronchoconstriction and increased respiratory secretions, abdominal pain, miosis, visual disturbance, and rhinorrhea.[9] An alternative acronym sometimes used to describe the effects of excessive muscarine stimulation is *DUMBBELS* (diarrhea, urination, miosis, bronchorrhea, bronchoconstriction, emesis, lacrimation, salivation).

Do not use the correction of miosis to judge the atropine dose.

Treatment. Performing early upper GI decontamination is useful, although spontaneous vomiting may eliminate the need for this treatment.[9] Activated charcoal administration is potentially useful. The specific reversal agent for muscarine poisoning is atropine.[9] If clinical signs of excessive muscarine stimulation are present, administeratropine (0.2 to 2 mg/kg; 50% of the dose administered intravenously and 50% intramuscularly or subcutaneously) slowly and progressively to effect using the drying of the oral and respiratory secretions as the clinical endpoints.[9] Do not use the correction of miosis to judge the atropine dose since by the time the pupils return to normal, most patients have received too much atropine, resulting in potentially adverse cardiovascular effects.[9] Intravenous crystalloids are usually sufficient to control any hypotension that develops.[9]

Isoxazole Derivatives

Amanita muscaria and A*manita pantherina* are the principal North American mushroom species associated with poisoning from isoxazole derivatives.[9] Given the popular recreational use of these mushrooms by people, it is surprising that poisoning in companion animals is poorly documented.[9]

Ibotenic acid and muscimol, the principal psychoactive isoxazole derivatives present in these mushrooms, alter visual perception rather than cause true hallucinations in people.[9]

Ibotenic acid, a CNS glutamate acid receptor agonist, acts as a CNS stimulant; muscimol, a CNS $GABA_B$ agonist, acts as a CNS depressant and sedative.[9] In people, the primary effects are periods of CNS stimulation and depression that may alternate and may manifest as periods of manic excitement followed by periods of somnolence and deep sleep. Clinical signs typically associated with poisoning in people include dizziness, ataxia, euphoria, muscle twitches, and initial psychic stimulation followed by dream-filled sleep.[9]

Treatment. Treatment consists of upper GI decontamination and supportive measures, such as observation, confinement in a dark and quiet cage, and possibly sedation. Use all hypnotic drugs with caution because the isoxazole derivatives potentiate their effects.[9]

Psilocybin and Psilocin

Because of its popularity as a recreational drug, this group of mushrooms, know as *hallucinogenic* or *magic mushrooms*, occasionally causes poisoning in dogs.[3] Important genera involved in poisoning include *Psilocybe, Panaeolus, Copelandia, Gymnopilus, Pluteus*, and *Conocybe.*[9] The principal toxins in these mushrooms are psilocybin and psilocin, which have LSD-like properties.[9] These compounds typically produce a transient (less than 12-hour duration), dysphoric, and sympathomimetic syndrome. Coingestion of other drugs of abuse such as LSD, PCP, and marijuana is common in people and is a potentially important consideration in veterinary patients.[9]

Common clinical signs, which develop a half an hour to four hours after ingestion, include anxiety, aggression, disorientation, visual hallucinations (*e.g.* following and biting at imaginary flies, pointless barking), weakness, mydriasis, tachycardia, and hyperreflexia.[3,9] Hypertension, hyperthermia, or convulsions may occur, and patients may become comatose in cases of extreme overdose. However, trauma caused by altered behavior is usually the greatest and most immediate threat to life.[3,9]

Treatment. Emergency GI decontamination in a conscious patient poisoned by these mushrooms may be difficult because of the patient's altered behavior and aggression. An easier option may be gastric lavage after anesthesia and placement of a cuffed endotracheal tube.[9] The main potential difficulty associated with anesthesia is the induction because of the dysphoric, and potentially aggressive, mental state of the patient. Prior sedation with a benzodiazepine (0.5 to 1 mg/kg diazepam intravenously or 1 to 4 mg/kg rectally) or an alternative induction technique, such as using an induction chamber, may be required. The use of induction chambers carries with it the increased risks associated with decreased access to the patient, so their use with dysphoric patients requires careful clinical judgment.

Treatment usually consists of supportive care. Since the most immediate concern is preventing accidental trauma, often the most successful supportive care is placing the animal in a quiet, dark, padded cage in the presence of its owner.[9] Warn the animal's owners and handlers of the potential for aggressive behavior. If sedation is required, a benzodiazepine (0.5 to 1 mg/kg diazepam intravenously or 1 to 4 mg/kg rectally) can be administered.

GI irritants

Numerous mushroom genera are GI irritants (*Table 1*).[9] For the most part, the toxic principles involved are unknown,[9] although idiosyncratic and allergic mechanisms have been proposed. Typically, clinical signs of acute GI upset occur within two hours of ingestion and consist of malaise, weakness, nausea, vomiting, and diarrhea.[9] The greatest risk associated with poisoning by these mushrooms is fluid and electrolyte imbal-

ance. Most cases are mild and usually resolve without treatment within 24 hours. If required, supportive care would consist of subcutaneous or intravenous crystalloids. The administration of oral GI protectants could be considered once vomiting has ceased.

Orelline and Orellanine

While *Cortinarius* species exist in North America, no poisoning has been recorded to date.[9] European and Japanese species from this genus cause acute, irreversible tubulointerstitial nephritis and acute renal failure.[9]

Prevention

As with most poisonings, the best method of controlling mushroom poisonings is preventing exposure. This means that only those who are knowledgeable about mushroom identification should collect wild-growing mushrooms for consumption. Dogs should be prevented from consuming mushrooms or roaming when they are being exercised. As with most poisonings, prompt upper GI decontamination and supportive care are critical elements of treatment. VM

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Phenylpropanolamine toxicosis in dogs and cats

Judy K. Holding, DVM, RN

Phenylpropanolamine (PPA) is a sympathomimetic drug used in dogs and cats primarily to treat urinary incontinence secondary to urethral sphincter hypotonia. It is labeled for use in dogs and is available as a solution in 25- and 50-mg/ml concentrations (Proin Drops—PRN Pharmacal); in chewable 25-, 50-, and 75-mg tablets (Proin—PRN Pharmacal, Propalin—Vétoquinol, Uricon—Neogen Corporation, Uriflex-PT—Butler Schein Animal Health); and as a 75-mg timed-release capsule (Cystolamine—Veterinary Product Laboratories).[1] PPA is classified as a list 1 chemical (can be used to manufacture methamphetamine) in the United States. Restrictions regarding its sale may vary among states, and in some states it may be a controlled substance.[1]

Historically in people, PPA was used as a decongestant and anorectic. It was removed from both over-the-counter and prescription use in the United States in 2000 because of data that suggested PPA increases the risk of hemorrhagic stroke in people.[2] It has since also been removed from the market in Canada.

Pharmacokinetics and Mechanism of Action

PPA is readily absorbed orally, with an oral bioavailability of approximately 98% in dogs.[3] In people, the onset of action is rapid, occurring within 15 to 30 minutes. It is widely distributed into multiple tissues and fluids, including the central nervous system (CNS). Approximately 80% to 90% of the drug is excreted unchanged in the urine within 24 hours of dosing.[1] The serum half-life in dogs is approximately three to four hours.[3] Clinical effects may persist well beyond what is expected based on the half-life.[4]

The recommended dosage for the immediate-release forms in dogs is 1 to 2 mg/kg given orally b.i.d.[5] The dose using the time-release 75-mg capsules is one-half capsule given orally once a day for dogs weighing < 40 lb (18.2 kg), 1 capsule given orally once a day for dogs weighing 40 to 100 lb (18.2 to 45.5 kg), and 1.5 capsules given orally once a day for dogs weighing >100 lb

(45.5 kg).[6]

The exact mechanism of PPA's action has not been determined. It is thought that it directly stimulates alpha-adrenergic receptors and indirectly stimulates both alpha-adrenergic and beta-adrenergic receptors by causing the release of norepinephrine.[1] It acts primarily on peripheral alpha receptors, with a weak effect on beta receptors.[7] Other pharmacologic effects of PPA include vasoconstriction, mild CNS stimulation, decreased nasal congestion, and decreased appetite. It also increases urethral sphincter tone.[1]

Toxicity

Adverse effects can potentially be seen at therapeutic doses and include restlessness, urine retention, anorexia, tachycardia, and hypertension. Stroke-like clinical signs have been reported rarely in dogs at therapeutic doses of PPA.[1]

The most common clinical finding of PPA toxicosis is hypertension secondary to peripheral vasoconstriction. A reflex bradycardia can be seen.[4] Other clinical manifestations of toxicosis may include piloerection, vomiting, tachypnea, anxiety or agitation, hyperthermia, tachycardia, tremors, and potential seizures.[1]

In one case report, a 5-year-old dog developed tachypnea, tachycardia, and ataxia after ingesting about 48 mg/kg of PPA.[8] Diagnostic test results (electrocardiography, echocardiography, creatine kinase activity, and cardiac troponin concentration) revealed areas of focal myocardial necrosis and multiform ventricular tachycardia consistent with myocardial damage from infarction or direct catecholamine-induced myocardial toxicity. During hospitalization, the dog developed ventricular tachycardia that was successfully treated with lidocaine. Enalapril and atenolol were also administered and continued after discharge. The owners were instructed on discharge to restrict the dog's activity. All abnormalities resolved within six months.[8]

The most common clinical finding of PPA toxicosis is hypertension secondary to peripheral vasoconstriction

ASPCA APCC Data

From 2003 to 2011, the ASPCA Animal Poison Control Center (APCC) database contains 823 cases of PPA exposures; 97% of the cases involved dogs, 3% cats, and < 1% birds.[4]

Only single-exposure cases were included. One cat receiving 2.8 mg/kg of PPA developed no signs.[4] Another cat that ingested 9.1 mg/kg presented with vomiting and mild hypertension, and a third cat that ingested 13.8 mg/kg developed moderate hypertension and tachypnea.[4]

In dogs, doses of 2.8 and 6.8 mg/kg resulted in mild hypertension and bradycardia.[4] Ingestion of > 15 mg/kg often resulted in significant cardiovascular signs.[4] At 16.6 mg/kg, a dog developed agitation, moderate hypertension, and ventricular tachycardia.[4] Ingestion of a similar dose at 16.7 mg/kg resulted in severe hypertension that responded to administration of acepromazine[4] After ingestion of 43 mg/kg, one dog developed anxiety, severe hypertension, and bradycardia.[4] Both acepromazine and nitroprusside were administered to control the hypertension. Final outcomes were not obtained in these cases.

Decontamination

Because of the rapid onset of action, emesis, using 3% hydrogen peroxide (2 ml/kg orally with a maximum of 50 ml) or apomorphine (0.03 mg/kg intravenously; or, in the conjunctival sac, 0.25 mg/kg after dissolving the tablet in saline solution), may be attempted within the first

10 to 15 minutes of exposure in animals not exhibiting clinical signs.[1] After, or in lieu of, emesis, activated charcoal (1 to 2 g/kg orally) with a cathartic such as sorbitol may be given.[9] The decision to give charcoal should be based on the dose of PPA ingested, weighing the benefit of activated charcoal with the potential risks for aspiration and the development of hypernatremia.

Monitoring and Treatment

Observe for CNS signs such as agitation or restlessness. Heart rate and rhythm, blood pressure, and body temperature should be monitored carefully. If marked hyperthermia is present, monitor for the development of disseminated intravascular coagulation. When hyperthermia is marked, cooling techniques should be instituted. If ventricular arrhythmias are detected, an echocardiographic examination should be considered.

Nitroprusside can be used to treat hypertension (1 to 2 µg/kg/min; increase the dose incrementally every three to five minutes, if necessary, until desirable blood pressure is achieved).[1] If nitroprusside is unavailable, a low dosage of acepromazine may be given (0.02 mg/kg intravenously) and increased in small amounts to the desired effect.[10] Phenothiazines are also effective for the anxiety or agitation that can be seen.

Bradycardia is usually a reflex mechanism that does not require specific intervention and is expected to resolve with correction of hypertension.

If marked supraventricular tachycardia is present, a beta-1-specific beta-blocker can be used, such as esmolol at 0.2 to 0.5 mg/kg given intravenously over one to two minutes or 25 to 200 µg/kg/min as a constant-rate infusion.[1] Propranolol, a nonspecific beta-blocker, should be avoided since blockade of beta-2 receptors may worsen any hypertension that is present. Ventricular arrhythmias may be treated with lidocaine or other appropriate antiarrhythmics. Intravenous fluids should be administered to maintain hydration, provide venous access, and promote adequate renal function. Fluids should be administered judiciously when hypertension is present. Other supportive measures should be instituted as needed.

Depending on the dose, clinical signs may persist up to 48 hours. Ideally, patients should be monitored in the hospital until they are not exhibiting any clinical abnormalities and are not receiving any medications for CNS or cardiovascular signs for six to eight hours. If a patient has experienced marked ventricular arrhythmias, follow-up echocardiographic and electrocardiographic examinations may be indicated. With appropriate symptomatic treatment, a full recovery is expected. VM

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