Common Hazards for Cats

Tina Wismer, DVM, DABVT, DABT
ASPCA Animal Poison Control Center
Urbana, IL

Alpha lipoic acid

Alpha lipoic acid is a fat-soluble, sulfur-containing, 'vitamin-like' antioxidant. It may also be called lipoic acid, thioctic acid, acetate replacing factor, biletan, lipoicin, thioctaid or thioctan. Alpha lipoic acid is found naturally in a variety of foods such as yeast and liver. Spinach, broccoli, potatoes, skeletal muscle and organ meats like the heart and kidney are also good sources. Alpha lipoic acid has been used to treat amanita mushroom poisoning, diabetic polyneuropathy, cataracts, glaucoma, and ischemia-reperfusion injury. Alpha lipoic acid is an antioxidant in fat and water soluble tissues. It increases intracellular glutathione, regenerates ascorbic acid, vitamin E, coenzyme Q10, and NADPH. It forms stable complexes with copper, manganese, and zinc, as well as protecting against glycation. Alpha lipoic acid is synergistic with insulin, causing decreased blood sugar and increasing liver glycogenesis, and facilitates glucose uptake into cells.

Alpha lipoic acid is frequently sold as 100 or 300 mg capsules. It is readily absorbed and has a 87%-90% bioavailability. Peak plasma levels occur within two to four hours. Evidence points to a strong first pass effect, even though the bioavailability is high. Pre-existing liver disease can limit metabolization. Alpha lipoic acid is primarily excreted renally. The therapeutic dose for cats is 1-5 mg/kg, with a maximum dose of 25 mg/day. The minimum toxic dose for cats is 13 mg/kg. At 30 mg/kg, neurologic signs and mild hepatocellular damage can occur.

Clinical signs of toxicity include vomiting, ataxia, hypersalivation, tremors and hypoglycemia. Seizures can occur and symptomatic animals should be monitored for acute renal failure. Clinical signs can occur 30 minutes to several hours post-ingestion. Decontamination should be performed within an hour of ingestion. Baseline laboratory values for blood glucose, liver enzymes, BUN, creatine and electrolytes should be obtained. Treatment is primarily symptomatic: control hypoglycemia, support liver function, correct dehydration if present, control vomiting, tremors and seizures.

Acetaminophen

Acetaminophen (Tylenol®, non-aspirin pain reliever, APAP) is a synthetic non-opiate derivative of p-aminophenol. APAP's exact mechanism of action is unknown, but it is acts primarily in the CNS to increase the pain threshold and may also inhibit chemical mediators that sensitize the pain receptors to mechanical or chemical stimulation. The antipyretic activity of APAP is achieved by blocking the effects of endogenous pyrogens by inhibiting prostaglandin synthesis.

Acetaminophen is rapidly and almost completely absorbed from the GI tract. Peak plasma levels are seen at 10-60 minutes (60-120 min for extended release). APAP is distributed into most body tissues with the highest concentrations in the peri-portal zone of the liver and the renal medulla. Elimination is capacity-limited. The parent compound is relatively safe, but the metabolites are highly toxic. Two major conjugation pathways are used to metabolize APAP by most species (P-450 metabolism followed by glucuronidation or sulfation). Acetaminophen-induced hepatoxicity and nephrotoxicity is due to the formation of the oxidative metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). Glutathione can conjugate and neutralize NAPQI, but when glutathione stores are depleted, NAPQI binds to sulfhydryl groups on the hepatic cell membrane and damages the lipid layer. Another metabolite, PAP (para-aminophenol), appears to be responsible for methemoglobinemia and Heinz body formation.

Methemoglobin values increase within 2-4 hours, followed by Heinz body formation. Clinical signs include depression, weakness, tachypnea, vomiting, methemoglobinemia, hypothermia, facial or paw edema and death. Liver necrosis is less common in cats than in dogs. Clinical signs of methemoglobinemia may last 3-4 days. Hepatic injury may not resolve for several weeks. No dose is safe in cats since they are deficient in glucuronyl transferase.

Early decontamination is most beneficial. Emesis is usually unrewarding. Activated charcoal adsorbs APAP and may need to be repeated, due to enterohepatic recirculation. A cathartic should also be used, unless the animal is dehydrated or has diarrhea. Monitor liver values and for the presence of methemoglobinemia. ALT, AST and bilirubin may rise within 24 hours after ingestion and peak within 48 to 72 hours.

Symptomatic patients need initial stabilization, including oxygen if dyspneic. Treatment involves replenishing the glutathione stores and converting methemoglobin back to hemoglobin. N-acetylcysteine (Mucomyst®, NAC) is a precursor in the synthesis of glutathione and can be oxidized to organic sulfate providing sulfhydryl groups that bind with APAP metabolites to enhance elimination. An initial oral loading dose of 140 mg/kg (dilute to 5% in dextrose or sterile water) is given, followed by 70 mg/kg PO QID for 7 treatments, or longer if still symptomatic. If the cat is already symptomatic, a loading dose of 280 mg/kg is given. A two-to-three hour wait between activated charcoal and PO administration of NAC is needed, since activated charcoal will adsorb NAC. Adverse effects of the oral route include nausea and vomiting. Some brands of NAC are labeled for IV use. Dilute to 5%, and give

slow IV over a period of 15 to 20 minutes. Fluid therapy is used to correct dehydration and for maintenance needs, not for diuresis. Whole blood transfusion may be necessary to increase oxygen carrying capacity, but the cat must be monitored for volume overload.

Ascorbic acid provides a reserve system for the reduction of methemoglobin back to hemoglobin; however, ascorbic acid has questionable efficacy and may irritate the stomach. Cimetadine, an inhibitor of cytochrome p-450s, traditionally has been recommended in treating APAP toxicosis. It has now been demonstrated that cimetidine blocks one of the only pathways that cats have to convert methemoglobin back to hemoglobin. For hepatic injury, s-adenosylmethionine (SAMe, Denosyl-SD4®) at 20 mg/kg/day shows a positive effect for treatment of APAP toxicosis. Prognosis is good if the animal is treated promptly. Animals with severe signs of methemoglobinemia or with hepatic damage have poor to guarded prognosis.

Ethylene glycol

Ethylene glycol is most commonly thought of as automotive radiator antifreeze, but ethylene glycol is also present in high concentrations in many brake fluids and aircraft deicers. In addition, ethylene glycol is often used in condensers, heat exchangers, home solar units and portable basketball goal post bases. Ethylene glycol may also be used to winterize toilets in recreational vehicles and summer homes in colder latitudes. Ethylene glycol is commonly present as a component in household paints, but it is rarely present in concentrations above 10%. Inks, ink pads, polishes, finger moistening compounds (e.g. Tacky Finger®), and other stationery supplies may contain high levels of ethylene glycol, but have small volumes.

Unfortunately, reliable toxic doses of ethylene glycol have not been established for most animals, including cats. Much of the acute toxicity data available is based on doses that cause early deaths from acidosis/intoxication and do not take into account the fact that many animals may survive the initial stages of toxicosis only to succumb to kidney failure days later. Because of this, any suspected oral exposure of a cat to ethylene glycol should be considered a potential toxicosis, and steps should be taken to attempt to determine the extent of the exposure. When doubt still exists, the only prudent recourse is to treat as if the ingestion was potentially toxic.

Ethylene glycol is a very potent alcohol and many of the early signs relate to severe alcohol intoxication. Ethylene glycol is broken down into metabolites (e.g. oxalic acid) that cause acidosis and damage to the kidney tubules, resulting in renal failure. Because of the different mechanisms involved in ethylene glycol toxicosis, clinical signs frequently change throughout the course of the toxicosis. The initial neurologic signs begin within 30 minutes and can last up to 12 hours. This stage may not be noticed by the cat owner. The cat may be ataxic and disoriented. Coma and death may occur during this stage, or the cat may appear to partially or fully recover over 3-6 hours. By 6-12 hours, the neurologic status of the cat may again deteriorate due to development of severe metabolic acidosis from ethylene glycol metabolites. Usually see marked CNS depression, stupor or coma. Seizures are possible. Oliguric renal failure can be seen as early as 12 hours in cats, but generally within 24-72 hours following exposure. Azotemia, depression, anorexia, vomiting, abdominal pain, oral ulcers, and oliguria progress to anuria. Urinalysis may reveal low urine specific gravity, glucosuria, and calcium oxalate crystaluria (absence of crystalluria does not rule out the possibility of EG toxicosis*)*. Seizures are possible. Clinical pathologic abnormalities include increased osmolal gap and anion gap, hyperglycemia, hyperkalemia, decreased blood pH, and hypocalcemia. BUN and creatinine become elevated but usually not before 12 hours post exposure.

Diagnosis is based on history, clinical signs, and confirmatory laboratory testing. Cats are much more sensitive than dogs to ethylene glycol. There are two available patient side ethylene glycol tests: Catachem and Kacey. The Catachem test is a colormetric qualitative test. It will be positive for any *cis-1*-diol (ethylene glycol, propylene glycol, glycerol, sorbitol, etc). It has both canine and feline tests. The Kacey strip test will be positive for any alcohol (see above, plus ethanol, methanol, etc.). It has both canine and feline tests on the same strip. The most reliable means of diagnosing ethylene glycol exposure would be having ethylene glycol levels run at a human hospital on a STAT basis. Any level above 20 mg/dl in cats should be considered significant. Measuring anion gap (>25 mEq/L) or serum osmolality (> 20 mOsm/kg) may assist in diagnosing ethylene glycol toxicosis. Observation, via Wood's lamp, of fluorescence in urine, stomach contents or on paws/muzzle may suggest exposure (fluorescein dye is added to automotive antifreeze to help in detecting radiator leaks).

Treatment of ethylene glycol toxicosis must be timely and aggressive. Failure to institute appropriate therapy within the first several hours may result in irreversible renal damage or death of the cat. Emesis and activated charcoal are somewhat controversial, as aliphatic alcohols are not thought to be well adsorbed by charcoal. Symptomatic cats should be stabilized as needed. Seizures can be controlled with diazepam or barbiturates, but care must be taken to minimize any further CNS depression. Intravenous fluids therapy is the cornerstone of treatment, especially in symptomatic cats. High infusion rates of crystalloids are necessary to correct dehydration and hypoperfusion; fluid ins and outs should be monitored to avoid fluid overload and possibly pulmonary edema. Treatment of acidosis and renal failure may be required. Oliguric or anuric cats may require peritoneal dialysis.

Intravenous ethanol and fomepizole (4-MP, 4-methylpyrazole, Antizol-Vet™) have been used successfully in the management of ethylene glycol toxicosis in animals and humans. The primary goal of using these compounds is to delay the breakdown of ethylene glycol to its more toxic metabolites, allowing the parent compound to be excreted in the urine unchanged.

Ethanol has the advantages of being inexpensive and readily available, but it has some serious drawbacks, including worsening of metabolic acidosis and CNS depression, making evaluation of degree of ethylene glycol toxicosis difficult. Additionally, ethanol

treatments are time-intensive and require constant patient monitoring because of the severe side effects. The preferred treatment regime would be to administer 8.6 ml/kg (600 mg/kg) of a 7% (70 mg/ml) ethanol solution and then maintain at 1.43 ml/kg/hr (100 mg/kg/hour), up to 200 mg/kg/hr as a constant rate infusion. The cat must be constantly monitored and the dosage adjusted to prevent severe respiratory depression and acidosis. The other method of ethylene glycol treatment would be to make a 20% ethanol solution. Cats are given 5.0 ml/kg every 6 hours for 5 treatments, then every 8 hours for 4 treatments.

Fomepizole has been approved for use in dogs only. Unlike ethanol, fomepizole will not cause hyperosmolality or metabolic acidosis. At dosages used in dogs, fomepizole is ineffective in treating feline ethylene glycol toxicosis. Cats require much higher doses to treat ethylene glycol toxicosis (125 mg/kg, then 31.24 mg/kg at 12, 24 and 36 hrs). Unfortunately, this regimen was successful only if initiated within 3 hours of ethylene glycol exposure. At 4 hours post exposure, fomepizole was unsuccessful in preventing death from ethylene glycol toxicosis, however, so was ethanol.

Treatment should be continued until cats are clinically normal and have had at least 24 hours with normal renal function and acid base parameters. The prognosis for recovery depends on degree of exposure, length of time between exposure and treatment, and aggressiveness of treatment. Surviving cats may fully recover or may have residual renal insufficiency requiring lifetime maintenance. The presence of oliguria/anuria indicates a grave prognosis.

Lily

Members of the true lily family (Lilium and Hemerocallis) have been shown to cause acute renal failure in cat. Some examples of true lilies include: Easter lilies (L. longiflorum), tiger lilies (L. tigrinum), rubrum or Japanese showy lilies (L. speciosum, L. lancifolium), and day lilies (H. species). The toxic principle is unknown, but is known to be water soluble. Even minor exposures (a few bites on a leaf, ingestion of pollen, etc.) may result in toxicosis, so all feline exposures to true lilies should be considered potentially life-threatening and should merit aggressive clinical intervention.

Affected cats often vomit within a few hours of exposure, but the vomiting usually subsides after a few hours, during which time the cats may appear normal or may be mildly depressed and anorexic. Within 24 to 72 hours of ingestion, oliguric to anuric renal failure develops, accompanied by vomiting, depression, and anorexia. Elevations in blood urea nitrogen (BUN), creatinine, phosphorus and potassium are detectable as early as 12 hours post ingestion. In some cases, hypoglycemia and mild liver enzyme elevations may occur. Casts, proteinuria, glucosuria, and isosthenuria are usually detectable on urinalysis within 24 hours of ingestion, reflecting lily-induced damage to renal tubular cells. In severe cases, death or euthanasia due to acute renal failure generally occurs within 3 to 6 days of ingestion.

Treatment of lily cats includes decontamination (emesis, one dose activated charcoal with cathartic) and fluid diuresis at twice maintenance for 48 hours. If treatment is started within the first 18 hours after exposure, prognosis is good. Delaying treatment beyond 18 hours frequently results in death or euthanasia due to severe renal failure. Since the tubular injury from lily ingestion spares the renal tubular basement membrane, regeneration of damaged tubules may be possible. In severe cases, peritoneal dialysis may aid in managing renal failure until tubular regeneration occurs.

Venlafaxine

Venlafaxine (Effexor®) is a bicyclic antidepressant; it is a potent serotonin and noradrenaline reuptake inhibitor as well as a weak dopamine reuptake inhibitor. It is available as both an immediate release and extended release medication. While it is rare for cats to willingly ingest medications, cats seem to readily eat venlafaxine. Doses as low as 2-3 mg/kg can cause signs of serotonin syndrome. Mydriasis, vomiting, tachypnea, tachycardia, ataxia and agitation are the most common signs. Treatment would consist of emesis in asymptomatic individuals. Activated charcoal can be administered with a repeated dose in 4-6 hours if an extended release formulation was involved. Heart rate and blood pressure should be monitored. Acepromazine may be used for the agitation, and cyproheptadine (2-4 mg per cat, PO or rectally) may be useful in antagonizing the serotonin effects.

With ingestion of the extended release medication, cats can be symptomatic for up to 72 hours. Venlafaxine is lipid soluble, so intralipids can be used to decrease plasma levels and decrease treatment time. Liposyn, or any other 20% lipid solution can be given through a peripheral catheter. A bolus of 1.5 ml/kg is given, followed by 0.25 ml/kg/min for 30-60 minutes. This is repeated in four hours if the serum is clear. As an aside, venlafaxine will cause a false positive reaction for PCP on the OTC urine drug tests.

Vyvanse®

Vyvanse® (lisdexamphetamine) is one of the new medications used to treat ADHD in children. It is available in 20, 30, 40, 50, 60 and 70 mg capsules. Just like venlafaxine, cats are attracted to this medication. Lisdexamphetamine is a prodrug of dextroamphetamine. Amphetamines are stimulants of the CNS and cardiovascular system. Amphetamines stimulate alpha- and beta-adrenergic receptors, causing the release of endogenous catecholamines at synapses in the brain and heart.

Vyvanse is an extended release medication and signs may be delayed for several hours. Signs may last for 24-72 hours. The most common clinical signs in cats include hyperactivity, tremors, tachypnea and hyperthermia. Tachycardia, vomiting, diarrhea, hypertension, and seizures have also been reported.

As emesis is usually unrewarding in the cat, activated charcoal should be administered. Fluid therapy is important to enhance elimination and maintain CV stability. Agitation and hyperactivity respond best to phenothiazines. Diazepam can worsen dysphoria and is not recommended. Because part of the syndrome is related to serotonin excess, cyproheptadine (2-4 mg PO or per rectum) has been used to manage some of the CNS effects. If tachycardia persists after institution of sedation, cyproheptadine and fluid therapy, beta blockers may be used.

References

Connally HE, Thrall MA, Hamar DW. Safety and efficacy of high-dose fomepizole compared with ethanol as therapy for ethylene glycol intoxication in cats. J Vet Emerg Crit Care 2010; 20(2): 191-206.

Hill AS, Werner JA, Rogers QR, et al. Lipoic acid is 10 times more toxic in cats than reported in humans, dogs, or rats. J Anim Physiol. A. Anim. Nutr 2004; 88: 150-6.

Hillyard SG, Barrera-Groba C, Tighe R. Intralipid reverses coma associated with zopiclone and venlafaxine overdose. European Journal of Anaesthesiology 2010; 27(6): 582–3.

McConkey SE, Cribb A. The Mechanism of Acetaminophen-Induced Toxicity in Dogs and Cats. Proceedings of the ACVP/ASVCP, San Antonio, TX, 2008.

Rumbeiha WK, et al. A comprehensive study of Easter lily poisoning in cats. J Vet Diagn Invest 2004; 16: 527-541.

Villar D, et al. Ibuprofen, aspirin and acetaminophen toxicosis and treatment in dogs and cats. Vet Human Toxicol 1998; 40: 156-161.

Wismer T. Antidepressant Drug Overdoses. Vet Tech May 2006: 278-81.

Youssef H. Hyperactivity and Disorientation in a Cat. NAVC Clinicians Brief. Dec, 2006: 49-50, 56.