Toxins Affecting the Kidneys

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

Pesticides

Cholecalciferol is a Vitamin D3 analog. It alters calcium metabolism in the body, increasing intestinal absorption and renal tubular reabsorption of calcium and stimulating bone resorption. Clinical signs of intoxication usually develop within 12-36 hours. Early signs include lethargy, weakness, anorexia, polydipsia, polyuria, and vomiting, often with blood. Biochemical alterations include hyperphosphatemia within 12 hours and hypercalcemia within 24 hours of exposure and azotemia (both renal and pre-renal). The elevated calcium levels result in calcification of many tissues, notable renal tubules and walls of blood vessels. The elevated calcium also has a direct effect on kidney function, sometimes causing acute renal failure even without mineralizations.

Household and industrial

Ethylene glycol (EG) is present in automotive radiator antifreeze, brake fluids, aircraft deicers, condensers, heat exchangers, home solar units and portable basketball goal post bases. Ethylene glycol may also be used to winterize toilets in RVs and summer homes in colder latitudes. Cats, rabbits and humans are the most sensitive to EG, with dogs, cattle, pigs and rodents having an intermediate sensitivity. It is important to remember that EG is a potent alcohol and many of the signs of toxicosis will relate to severe alcohol intoxication. Because of the different mechanisms involved in EG toxicosis, clinical signs frequently change throughout the course of the toxicosis. It is sometimes easier to break the clinical signs into 3 different stages, although considerable overlap between these stages may be seen and some animals will not experience each stage; death can occur at any stage. The stages are 1) neurologic—the initial inebriation due to the effects of alcohol on the CNS, 2) cardiopulmonary—due to severe acidosis and electrolyte disturbances, and 3) renal—due to renal tubular injury from calcium oxalate crystals. Treatment of EG 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 animal.

Phenol (carbolic acid, hydroxybenzene, oxybenzene) is a hydrolyzed form of benzene. Phenols are used for their antiseptic and local anesthetic properties. Dilute phenol solutions (0.1-4.5%) are found in sore-throat lozenges, throat sprays, gargles, gels, ointments, and lotions as a local anesthetic. Phenol destroys the outer layers of skin and is sometimes used as a chemical peel. Phenol is readily absorbed following inhalation, oral and dermal exposure. In dilute solutions, phenol is an irritant and inflammation may be seen at the site of absorption. In concentrations of 5% or more, phenol rapidly denatures all proteins with which it comes into contact. Dermal application of phenol can also cause systemic signs. Large doses can lead to muscle tremors, seizures, coma and death. Mortality associated with dermal exposure to phenol is greatly influenced by the surface area exposed as well as the concentration of the applied solution. Cats are more sensitive to phenol because of their limited glucuronide transferase activity. Oral phenol exposure in animals causes panting, profuse vomiting, diarrhea, salivation, and ataxia, which may progress to gastric ulcers, muscle fasciculations, and methemoglobinemia. Urinalysis abnormalities include albinuria, hematuria, green/black color, and the presence of casts.

Pine oil (arizole, oleum abietis, unipine, yarmor) is a component of many household cleaners and disinfectants. Pine-scented formulations contain small amounts of pine oil and have minimal toxicity compared with pure pine oil. Oral and dermal absorption of pine oil is considered to be poor. Pine oils are irritating to the mucous membranes, producing erythema of the oropharynx, mouth, and skin. Ingestion of pine oil may cause vomiting, CNS depression, tachycardia, nephritis, and fever. Less commonly seen signs include diarrhea, hypotension, bradycardia, ataxia, coma, renal failure, and myoglobinuria following large ingestions. Pulmonary toxicity may be caused by either aspiration, or chemical pneumonitis resulting from absorption of pine oil from the GI tract with subsequent deposition in the lung. Cats are deficient in certain types of glucuronyl transferase activity, making them more susceptible than other species to pine oil toxicoses. A cat that ingested about 100 ml of Pinesol® (20% pine oil, 10.9% isopropanol) developed severe depression, ataxia, unresponsive pupils, and died. Autopsy revealed pulmonary edema, acute centrilobular hepatic necrosis, and total renal cortical necrosis.

Pharmaceuticals

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. Decreased prostaglandins mean decreased pain but also decreased secretion of the protective mucous layer in the stomach and small intestine and vasoconstriction in gastric mucosa. NASIDs inhibit renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. NSAIDs have a narrow margin of safety. GI ulcers and renal failure can be seen after an acute ingestion. Cats are thought to be twice as sensitive as dogs due to their limited glucuronyl-conjugating capacity.

There are many other renal toxic pharmaceuticals including: sulfonamides, tetracyclines, amphotericin B, cisplatin and most of the heavy metal chelators. Alpha lipoic acid is a neutraceutical that can also cause renal failure.

Metals

Arsenic can be found in some fungicides, herbicides, pesticides and ashes from chromated copper arsenate (CCA) treated lumber. Arsenic interferes with a variety of enzyme systems within the body, resulting in disruption of cellular homeostasis that can result in peracute death within hours of exposure. Arsenic is readily absorbed via ingestion and has a predilection for skin, nails, hooves, feathers, sweat glands and hair. Bloody vomiting and/or diarrhea due to extensive necrosis and hemorrhage of the gastrointestinal tract characterize acute arsenic toxicosis. Damage to capillary endothelium results in fluid and blood leakage, hypovolemia, dehydration, hypotension and shock. Cardiac arrhythmias, pulmonary edema and multi-organ failure secondary to acute cardiovascular collapse are possible. Later signs may include lethargy, anorexia, fever, polyuria progressing to anuria, tremor, hypothermia, stupor and death. Treatment of arsenic toxicosis entails removal of the arsenic source, symptomatic care and, potentially, chelation with British Anti-Lewisite (BAL).

Mercurial salts are present in elemental, inorganic and organic forms. Inorganic mercury compounds have been used historically in diuretics, antibacterials, antiseptics, ointments, laxatives, and antisyphilitic agents. Mercury ions bind to sulfhydryl groups and also have an affinity for phosphoryl, carboxyl, amide and amine groups. This impairs the structure and function of key proteins and enzymes, and alters receptor affinities and cellular metabolism. Inorganic mercury salts are corrosive and nephrotoxic following ingestion. Salivation, abdominal pain, watery bloody diarrhea, proteinuria, and acute renal failure may occur and potentially fatal hypovolemic shock may result. Perform chelation in symptomatic patients (DMSA, BAL, d-penicillamine).

Plants

Grapes/raisins (Vitis sp.) can cause renal failure in dogs. At this time the mechanism of action and toxic principle are unknown. Histopathologic examination has shown proximal renal tubular degeneration or necrosis with the basement membrane remaining intact. The distal convoluted tubules are usually less frequently and less severely affected. Some dogs are exposed and never develop signs and some only develop mild GI signs and recover. Vomiting usually begins within 6 hours of ingesting the grapes/raisins. BUN and creatinine begin to elevate in 12-18 hours. Dogs developing severe oliguria or anuria generally were poorly responsive to attempts to increase urine production (mixed results with peritoneal and hemodialysis). If renal values are normal at 48 hours, the animal can be weaned off fluids and sent home.

True lilies of the Lilium and Hemerocallis genera (Easter lilies, tiger lilies, day lilies, etc.) can cause acute renal failure in cats. The water soluble toxic principle is unknown. Even minor exposures (bite on a leaf, ingestion of pollen) may result in toxicosis, so all feline exposures to lilies should be considered potentially life-threatening. It should be noted that not all plants with “lily” in the name are true lilies. Cats often begin vomiting within a few hours after exposure. Within 24 to 72 hours of ingestion, oliguric to anuric renal failure develops, accompanied by depression, anorexia, and dehydration. Elevations in BUN, creatinine, P and K+ are detectable as early as 12 hours post ingestion. Creatinine elevations may be especially high. Abundant 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.

Cortinarius sp. mushrooms contain orellanine, a nephrotoxic compound. These bright rust-brown or orange-brown mushrooms occur throughout the U.S. and Canada. Orellanine is not destroyed by drying or cooking. It inhibits alkaline phosphatase which in turn interrupts the production of ATP. Lesions are limited to the kidney (tubulointerstitial nephritis). There can be a latent period of 36 hours to 20 days before the onset of symptoms in people. Anorexia, vomiting, diarrhea, PU/PD, lethargy, and muscle pain can be followed by oliguric or anuric renal failure. Due to the long lag time, GI decontamination is limited. Monitor for renal failure, hypotension, arrhythmias, respiratory depression, hypoglycemia, electrolyte disturbances, and hypoxia. Forced diuresis should NOT be done because it may increase renal damage. Peritoneal dialysis and kidney transplants are performed in humans. Outcome is based on the amount of toxin ingested, but a great deal of variability exists. A shorter latent period correlates with a poorer prognosis.

Mycotoxins

Ochratoxin A (OA) is a potent nephrotoxin produced by several species of Aspergillus and Penicillium molds. Monogastric species are much more sensitive to ochratoxins than ruminants. Ochratoxicosis is usually associated with the feeding of contaminated barley, but wheat, oats, corn, beans, peanuts, hay, and green coffee beans have tested positive. OA is a competitive inhibitor of protein synthesis, induces lipid peroxidation and interferes with carbohydrate metabolism. OA causes degeneration of proximal renal tubules and bile duct proliferation. OA can be tested for in feed, liver or kidney and metabolites can be found in milk or urine. Treatment is symptomatic and supportive.

Citrinin is another mycotoxin that can cause renal tubular necrosis. It is commonly found with ochratoxins. Most grains including wheat, oats, barley and corn can be affected. Within a few hours, protein, and glutathione (GSH) tissue levels are decreased and the respiratory capacity (uptake of O2) and the metabolic enzyme succinic dehydrogenase are inhibited. Treatment is symptomatic and supportive.

Miscellaneous

Any toxin that causes hemoglobinuria (pit viper venom, onions/garlic, brown recluse spiders, zinc) can cause hemolysis. Free hemoglobin is toxic to the kidney. Hemoglobinuria can induce acute tubular necrosis through the formation of hemoglobin casts. IV fluids should be started to combat hypovolemia and protect the kidneys. Toxin cause tremors/seizures can lead to myoglobinuria. Myoglobin, a monomer containing a heme molecule similar to hemoglobin, when excreted in the urine can precipitate, causing tubular obstruction and acute kidney injury.

References available upon request.