**TOP 20 TOXIC TITANS… AND HOW TO TREAT THEM: PART I** **SCIENTIFIC: TOXICOLOGY**

**Justine A. Lee, DVM, DACVECC**

## INTRODUCTION

Pet Poison Helpline, a 24/7 animal poison control located out of Minneapolis, MN, receives phone calls from both pet owners and veterinarians regarding toxicity cases from accidental or intentional misuse of over-the-counter (OTC) or prescription medications, common garden or outdoor toxins, and common household products. In this two part session, the top 20 small animal toxins seen by Pet Poison Helpline will be reviewed.

In veterinary medicine, the primary treatment for toxicant exposure should be decontamination and detoxification of the patient. The goal of decontamination is to inhibit or minimize further toxicant absorption and to promote excretion or elimination of the toxicant from the body. Decontamination can only be performed within a narrow window of time for most substances; therefore, it is important to obtain a thorough history and time since exposure. Decontamination categories may include ocular, dermal, inhalation, injection, gastrointestinal (GI), forced diuresis, and surgical removal to prevent absorption or enhance elimination of the toxicant. For further review on decontamination and specific treatment, attendees are referred to a veterinary toxicology book for more detailed review.

### Selective serotonin re-uptake inhibitors (SSRIs)

Selective serotonin re-uptake inhibitors (SSRIs) are a class of medications that are commonly used in human medicine for depression. Common examples include drugs like fluoxetine (Prozac® in human beings; Reconcile™ in veterinary medicine), citalopram (Celexa®), escitalopram (Lexapro®), paroxetine (Paxil®), and sertraline (Zoloft®). Other similar drugs include selective norepinephrine re-uptake inhibitors (SNRIs), which include common drugs like duloxetine (Cymbalta®), nefazodone (Serzone®), and venlafaxine (Effexor®). SNRI and SSRI drugs result in similar clinical signs of toxicosis, and therefore are treated the same. In veterinary medicine, SSRIs are used for a wide array of behavioral problems, including feline urine spraying, canine separation anxiety, lick granulomas, etc. SSRI drugs work by blocking the reuptake of serotonin in the pre-synapse, thereby increasing the levels of serotonin in the pre-synaptic membrane. In small animal patients, common clinical signs from SSRIs include sedation or central nervous system (CNS) stimulation, anorexia, and lethargy, even at therapeutic doses. Increases in levels of serotonin, even in small doses, may lead to serotonin syndrome. Clinical signs of serotonin syndrome include: CNS stimulation, vomiting, tremoring, seizures, hyperthermia (secondary to tremoring and seizuring), diarrhea, abdominal pain, and mydriasis (dilated pupils). Treatment includes decontamination (ideally done at a veterinarian, due to the rapid onset of clinical signs), activated charcoal, hospitalization for sedation (e.g., with acepromazine or chlorpromazine), temperature regulation, IV fluid therapy, and supportive and symptomatic care.

### Sleep aids

Sleep aids are often benzodiazepines or non-benzodiazepine hypnotics, and include drugs such as zolpidem (Ambien®) and eszopiclone (Lunesta®). These drugs work similarly to benzodiazepines (e.g., diazepam) as they potentiate GABA transmission, increasing frequency of chloride channel opening and resulting in inhibition of neuronal excitation. While these drugs result in sedation in humans, up to 40% of dogs ingesting toxic doses of sleep aids develop paradoxical CNS stimulation rather than expected depression. Clinical signs include CNS depression (e.g., depression, ataxia, weakness, paresis), CNS stimulation (e.g., hyperactivity, anxiety, agitation, panting, tremors), or even other signs like nausea, vomiting, diarrhea, and hyperthermia. Treatment includes decontamination, activated charcoal, and for those patients demonstrating signs of CNS stimulation, the use of sedatives or anxiolytics. In patients exhibiting CNS stimulation, benzodiazepines (e.g., intravenous diazepam) should *not* be used, as they may worsen the symptoms. Rather, the use of phenothiazines (e.g., acepromazine, chlorpromazine) or barbiturates (e.g., phenobarbital intravenously) should be used instead. In severe cases of respiratory or cardiac depression, the use of flumazenil, the reversal agent for benzodiazepines, can be considered.

### Amphetamines

Amphetamines are used for a variety of medical and illicit reasons. Legal forms include prescription medications for ADD/ADHD, weight loss, and narcolepsy, and include dextroamphetamine and amphetamine (Adderall®), D-amphetamine (Dexedrine®), methamphetamine (Desoxyn®), and lisdexamfetamine (Vyvanse®). Illegal forms of amphetamines include street drugs like methamphetamine, crystal meth, and ecstasy. This class of drugs acts as sympathomimetic agents, meaning they stimulate the sympathetic system. Amphetamines also cause stimulation of α and β-adrenergic receptors, and stimulate release of serotonin and norepinephrine; this results in increased

catecholamine stimulation in the synapse. Amphetamines also increase release of serotonin from the presynaptic membrane, resulting in serotonin syndrome. With amphetamine toxicosis, secondary stimulation of certain body systems can result in significant clinical signs: CNS (e.g., agitation, mydriasis, tremors, seizures), cardiovascular (e.g., tachycardia, hypertension), GI (e.g., vomiting, diarrhea, hypersalivating), and respiratory (e.g., panting). The oral lethal dose is low for amphetamines, and ranges from 10-23 mg/kg. Both clinical signs and treatment for amphethamine toxicosis are similar to SSRI toxicosis, and include IV fluids, cooling measures, sedation (e.g., with acepromazine or chlorpromazine), temperature regulation, blood pressure monitoring, and symptomatic and supportive care.

**Topical toxins**

One of the most dangerous topical toxins to be aware of is 5-fluorouracil (5-FU), which is a prescription anti-cancer medication used topically for humans with superficial basal cell carcinoma or actinic keratosis. Brand names include Efudex®, Carac®, Adrucil®, and Fluoroplex®. These drugs work by inhibiting DNA and RNA synthesis and production, and are rapidly absorbed from the gastrointestinal tract (GIT). Even tiny amounts can be very toxic, resulting in acute GI and CNS symptoms. The prognosis with ingestion is grave in cats and guarded in dogs (with a reported survival in dogs of approximately 25%). Clinical signs can often be seen within 30 minutes up to 6 hours, and death has been reported within 7 hours. Clinical signs include acute nausea, vomiting, hemorrhagic diarrhea, abdominal pain, sloughing of the GIT, ataxia, severe and non-responsive seizures, and severe dose-dependent myelosuppression affecting all cell lines (e.g., pancytopenia - leukopenia, thrombocytopenia, and anemia). A severe metabolic acidosis and evidence of multi-organ failure can be seen. Typically, decontamination is not effective due to rapid onset of clinical signs. Treatment is supportive and includes anti-convulsant therapy, anti-emetic therapy, IV fluids to maintain perfusion to both the GIT and CNS, temperature regulation, antibiotic therapy (to help prevent sepsis from severe leukopenia), monitoring of baseline blood work to evaluate bone marrow and organ function (e.g., CBC, chemistry, venous blood gas), and symptomatic and supportive care. Death typically occurs due to secondary complications such as sepsis, intracranial hemorrhage (from severe thrombocytopenia), increased intracranial pressure (from severe seizures), etc. In general, a CBC should be performed every 3-4 days for at least 18 days, as it takes up to 3 weeks before all cell lines in the bone marrow return to normal.

**Non-steroidal anti-inflammatory drugs (NSAIDS)**

NSAIDs are competitive inhibitors of prostaglandin synthesis (cyclooxygenase or “COX”) and result in decreased prostaglandin, which is important for normal homeostatic function (including maintaining renal blood flow, maintaining mucous production in the stomach, etc.). With NSAID toxicity, the GIT, kidneys, platelets, and CNS can be affected. Cats and certain breeds of dogs (e.g., German shepherds) seem to be more sensitive to NSAIDS, and must be treated aggressively. Common OTC human NSAIDS include drugs such as Advil®, Aleve®, certain types of Motrin®, etc. Common prescription veterinary NSAIDS include carprofen, deracoxib, etogesic, previcoxib, etc. Each NSAID has a different toxic dose. For example, ibuprofen results in GIT signs at doses as low as 16-50 mg/kg, while severe GI signs may be seen at 50-100 mg/kg. Renal compromise may be seen at doses of 100-250 mg/kg (resulting in potential acute renal failure), and fatalities have been reported at doses > 300 mg/kg. This differs tremendously from Aleve® (naproxen sodium), where severe clinical signs can be seen at doses as low as 5 mg/kg. At experimental doses of 22 mg/kg orally once a day for 3 days, perforation of the GIT has been documented with naproxen. Each NSAID has a different half-life, route of excretion, and toxic dose, and an animal poison helpline should be contacted to identify what specific NSAID and toxic dose was ingested. Treatment includes decontamination, the use of activated charcoal (often multiple doses due to enterohepatic recirculation), GI protectants, aggressive IV fluid therapy (to help maintain renal blood flow), anti-emetic therapy, and symptomatic and supportive care. With high doses, anti-convulsants may also be necessary if seizures develop.

**Insect bait stations**

Household ant and roach bait stations are rarely toxic, as the active ingredient is often a low-concentration of abamectin (a macrocylic lactone derivative in the same family as ivermectin). Certain breeds with the MDR-1 gene mutation (now known as the ABCB1-1Δ polymorphism), including collies, Border collies, old English sheepdogs, and collie-mixed breed dogs, may be more at risk when large amounts of bait stations are ingested. Typically, the plastic on the bait station is more of a problem, as it can result in GI signs or potentially foreign body obstruction (which ingested in large amounts).

**Fertilizers**
Fertilizers generally have a wide margin of safety, and result in mild GI signs when ingested directly from the bag. Ingestion of grass that had a fertilizer applied to it previously rarely results in serious toxicosis. When appropriately applied or diluted, these chemicals typically wash into the soil after rainfall, resulting in low-risk to patients.

**Xylitol**
Xylitol is a natural sweetener found in small quantities in certain fruit. Xylitol has gained recent popularity because it is sugar-free, and is often found in diabetic snacks, foods, baked foods, and popular gums and candies. Sugarless gums, particularly those with xylitol listed within the first five active ingredients, can result in severe toxicosis within 15-30 minutes of ingestion. Ingestion of xylitol results in an insulin spike in non-primate species, resulting in severe hypoglycemia. As each piece of candy or gum may contain various amounts of xylitol (ranging, on average, from 0.22 grams/piece to 1.0 grams/piece), it is imperative to calculate if a toxic dose has been ingested. Unfortunately, not all sources are disclosed by the company (e.g., how many grams of xylitol may be in each piece of gum). In general, doses > 0.1 g/kg are considered toxic and result in profound, sudden hypoglycemia from insulin stimulation treatment. Treatment includes decontamination, STAT blood glucose monitoring, dextrose supplementation, and IV fluid therapy as needed. With recent ingestion, decontamination should promptly be performed, provided the patient is not demonstrating any signs of hypoglycemia. Keep in mind that activated charcoal does *not* reliably bind to xylitol, and is not routinely recommended for this toxicity. Clinical signs of xylitol toxicosis include lethargy, weakness, vomiting, collapse, anorexia, etc. A blood glucose should be checked, and if hypoglycemic, a bolus of 1 ml/kg of 50% dextrose, diluted with an additional amount of 0.9% NaCl (in a 1:3 ratio) should be given IV over 1-2 minutes. Hypoglycemic patients should then be hospitalized for IV fluids [supplemented with dextrose (2.5 to 5% dextrose, CRI, IV)] and frequent blood glucose check should be performed every 1-4 hours. Higher doses (> 0.5 g/kg) of xylitol are associated with acute hepatic necrosis. Treatment for hepatotoxic doses includes decontamination, hepatoprotectants (e.g., s-adenosylmethionine), IV fluids, dextrose supplementation, anti-emetics, and supportive care (including liver enzyme monitoring), etc.

**Silica gel packs**
Silica gel packs, while commonly ingested by pets, rarely result in toxicosis as they have a wide margin of safety (despite their labeling of "Do not eat"). When ingested in large amounts, they can potentially result in foreign body obstruction; however, this is generally rare. Some types may contain iron (particularly types of oxygen absorbers found in jerky or rawhide bags), which can result in iron toxicosis in small dogs or when ingested in large amounts.

**Rodenticides**
One of the most common mistakes seen in the field of veterinary toxicology is assuming that each green or blue rat or mouse poison is a long-acting anticoagulant (LAAC) rodenticide. Several different classes of rodenticides also exist, and are commonly mistreated with Vitamin $K_1$ therapy inappropriately. Other types of rodenticides include bromethalin, zinc phosphide, and cholecalciferol rodenticides. *Bromethalin* works by uncoupling oxidative phosphorylation in the brain and liver mitochondria, resulting in cerebral edema (with clinical signs seen as ataxia, decreased mentation, tremors, seizures, etc.). *Phosphide* rodenticides result in the production of phosphine gas, which is toxic to humans also. When zinc phosphide combines with gastric acid (or the presence of food!), liberated phosphine gas is rapidly absorbed across gastric mucosa and distributed systemically, where it exerts its toxic effect. Clinical signs include severe GI signs (e.g., vomiting, bloat, abdominal pain, etc.), CNS signs (e.g., tremoring, seizuring), and pulmonary signs (e.g., pulmonary edema, tachypnea, etc.). More importantly, emesis – whether intentionally induced or occurring due to clinical signs - can result in poisoning to the pet owner or the veterinary professional. Clinical signs of nausea and difficulty breathing have been reported in humans exposed to secondary phosphine gas. Treatment with an antacid prior to emesis induction may help decrease the presence of phosphine gas. Also, emesis induction should always be performed in a well ventilated area (e.g., opening the car window if the patient vomits or inducing emesis outside or in a well-ventilated area). *Cholecalciferols* are the most deadly – and costly – to pets, as it results in severe hypercalcemia with secondary mineralization of the kidneys and soft tissues. This results in acute and potentially chronic renal failure, and must be treated aggressively with IV fluid therapy, calcium monitoring, and administration of steroids, diuretics, and bisphosphonates. Lastly, first and second generation *LAAC anticoagulants* result in inhibition of Vitamin K epoxide reductase, resulting in inactivation of clotting factors II, VII, IX, and X. Clinical signs and elevation in clotting factors [prothrombin (PT) or activated partial thromboplastin time (aPTT)] are not seen for 48 hours. Treatment includes decontamination, measurement of PT/PTT 48 hours post-ingestion, or prophylactic treatment with Vitamin $K_1$ for a minimum of 4 weeks. A recheck

PT should be performed 48 hours after the last administered dose; if prolonged, an additional 2 weeks of Vitamin $K_1$ therapy should be administered.

**CONCLUSION**

Pet owners should be appropriately educated on how to pet-proof the house, and be trained on what common household products and kitchen items are poisonous. Pet owners should also be appropriately educated on crate training to help minimize toxin exposure. Once a pet is exposed to a toxicant, it is imperative to determine if emesis is appropriate, and to understand when it may be contraindicated (e.g., symptomatic patient, delayed time since exposure, hydrocarbons, etc.). Knowledge of the underlying mechanism of action, the pharmacokinetics (including absorption, distribution, metabolism, and excretion), and the toxic dose of the toxicant are imperative in determining appropriate decontamination and therapy for the patient.

**References available upon request.**