V317
Topical Toxic Titans…and How to Treat Them!

Ahna Brutlag, DVM
Pet Poison Helpline, Bloomington, MN, USA

This lecture will cover "topical toxins," encompassing those products both **applied** topically to cats and dogs, as well as those topical preparations accidentally **ingested** by cats or dogs such as common over-the-counter and prescription creams, ointments, and transdermal patches.

Zinc Oxide Ointment

Topical zinc oxide is found in diaper rash creams (such as Desitin®) and other "skin protection" type products. Concentrations vary from 5–40%. In acute ingestions, elemental zinc toxicity is highly unlikely. Most animals will experience spontaneous but self-limiting vomiting following ingestion (thereby self-decontaminating). Symptomatic and supportive care may be warranted if vomiting or diarrhea becomes severe.

Corticosteroid Ointments and Solutions

Topical steroid ointments and ophthalmic preparations are commonplace products containing up to 1% hydrocortisone, betamethasone, or triamcinolone. Toxicity is unlikely following oral exposure to these products. Some animals may experience mild, self-limiting vomiting or diarrhea (likely as a result of the petroleum-based carrier). In some cases, dogs or cats have experienced self-limiting polyuria/polydipsia secondary to systemic absorption. Most often, no medical treatment is needed.

Antibiotic Ointments

Topical antibiotic ointments, such as Neosporin®, are common products around the home. They often contain a mixture of neomycin sulfate, bacitracin, and polymyxin sulfate. Acute ingestions may result in self-limiting vomiting, diarrhea, and abdominal pain. These signs are partially accredited to the petroleum-based carriers of the products rather than the antibiotics themselves. However, in large ingestions, the products may lead to an imbalance of normal gastrointestinal flora, thereby contributing to the GI signs mentioned. Treatment is symptomatic and supportive.

Tea Tree (Melaleuca) Oil

Tea tree oil (otherwise known as melaleuca oil) is an extract of the leaves of the Australian tea tree (*Melaleuca alternifolia*). This oil has proven antibacterial and antifungal properties and is found in numerous personal-care products such as face washes, shampoos, lotions and ointments. Exposures to these diluted products do not typically lead to toxicity. Tea tree oil is also touted as an insect repellant and antiparasitic compound. Toxicity most often occurs when well meaning owners apply 100% oil as a means of parasite control.

The oil is rapidly absorbed from both the skin and gastrointestinal tract. Common clinical signs of toxicity include weakness, ataxia, muscle tremors, central nervous system depression, and hypothermia. Signs will generally arise 2–8 hours following application and resolve within 1–2 days. While the exact range of toxicity is not well established, cases of toxicity following dermal administration of less than 10 mL of 100% oil on both dogs and cats have been reported to the Pet Poison Helpline.

An antidote is not available and treatment consists mainly of decontamination and supportive care. Bathing the animal with a de-greasing soap such as liquid hand dishwashing soap will aid in the removal of the oil from the skin. The administration of multiple doses of activated charcoal is advised following significant ingestion. Supportive care and baseline diagnostics should include the administration of intravenous fluids to maintain hydration, the monitoring of body temperature along with necessary thermal support, and the monitoring of vital signs, hepatic enzymes and serum electrolytes.

Nicotine Transdermal Patches

Nicotine transdermal patches may contain substantial amounts of nicotine. When an animal chews on a patch and compromises the rate-controlling structure, the majority of the nicotine may be quickly

released leading to a rapid onset of clinical signs. Individual patches contain anywhere from 7–114 mg of nicotine per patch. The total amount of nicotine contained within the patch will likely be greater than the amount it is designed to release. Hence, even used patches still contain some amount of nicotine and may pose a toxicity risk.

The oral LD 50 for nicotine in dogs is 9–12 mg/kg. Lethal dose data has not been reported in cats. However, it is common to find that dogs can tolerate significantly higher doses than this without fatality.

Signs of nicotine toxicity encompass multiple organ systems. Soon after ingestion, salivation and vomiting may occur. Nicotine acts as both a central nervous stimulant and a depressant. Therefore, in cases of severe toxicity, initial gastrointestinal irritation may be followed by systemic signs such as hypertension, tachycardia, tachypnea, hyperexcitability, mydriasis, tremors, and/or seizures. Delayed onset signs include neurologic depression, respiratory depression, ataxia, seizures and death.

Due to the rapid release of nicotine from damaged patches, treatment is typically focused on clinical signs versus patch removal. However, if the patch remains intact when ingested and is not removed, the release of nicotine could be very slow (many hours versus 1–2 hours) thus warranting removal via emesis, gastric lavage, or endoscopy.

Treatment is symptomatic and supportive as no antidote for nicotine toxicity is available. Heart rate and blood pressures should be monitored closely and treated as needed. Beta-blockers may be used for tachycardia. Severe CNS stimulation or seizures may be treated with diazepam, barbiturates, or phenothiazines. Intravenous fluid administration may increase the rate of nicotine excretion. Antacids are not recommended as the may increase nicotine absorption from the stomach.

Fentanyl Transdermal Patches

Fentanyl is a synthetic opioid analgesic which binds to *mu* receptors. It is 50–100 times more potent than morphine. The transdermal patch is designed to release a constant amount of drug over a fixed time period. However, once the internal structure of the patch is disturbed (i.e., chewed on), a large amount of drug may be quickly released. Fentanyl patches contain significantly more fentanyl than is designed to be released during therapeutic transdermal absorption. For example, Duragesic® 50 (Ortho-McNeil-Janssen Pharmaceuticals, Inc) patches are designed to release 50 *micro*grams of fentanyl per hour for a duration of 72 hours. However, this same patch holds a total of 5 *milli*grams of drug. "Spent" patches retain up to 84% of their fentanyl and may pose a lethal risk if ingested.

The most typical cause of fentanyl toxicity is due to ingestion of the patch. However, the most common cause of iatrogenic toxicity occurs during surgical procedures when cutaneous blood flow to the dermal patch site is significantly increased secondary to heating pads or warmed surgical tables.

Signs of toxicity vary between the species. Dogs tend to exhibit more classic opioid effects such as sedation and central nervous system depression, depression of cardiac and respiratory rates, miosis, and hypothermia. Cats are more likely to exhibit paradoxical central nervous stimulation and mydriasis.

Decontamination of pets ingesting fentanyl patches needs to be managed with care. Unless the ingestion of the patch less than 10 minutes prior, the induction of emesis at home/by the pet owner is not recommended due to the potentially rapid onset of central nervous system changes. If the induction of emesis is not possible given the pet's neurologic status, the patch may be removed via surgery or endoscope. Because these patches are designed to release small amounts of fentanyl over a period of days, patch removal is an important part of case management. Once removed, signs of toxicity should begin to resolve within 2–6 hours.

Naloxone may be administered for the reversal of respiratory and CNS depression. It often needs to be re-dosed every 30–60 minutes until the pet is able to support itself. Seizures may be treated with diazepam. Additional treatments such as intravenous fluids to support the cardiovascular system, thermal support, and mechanical ventilation may be necessary. Death following opioid toxicity is most often due to severe respiratory depression.

Salicylates (Aspirin, Oil of Wintergreen, etc.)

Salicylates are keratolytics and are used, in human medicine, for the topical treatment of acne, psoriasis, ichthyoses, dandruff, corns, calluses, and certain warts. Acetylsalicylic acid (ASA), better known as

aspirin, is commonly found in many over-the-counter and prescription analgesic ointments or liniments. Non-aspirin salicylates, such as salicylic acid, are found in over-the-counter topical acne control creams, lotions, sunscreens, facial masks, "medicated" face washes, and make-up (foundations and concealers). Such products may contain 1–5% salicylate. Methyl salicylate is found in concentrations up to 30% in over-the-counter and prescription liniments such as Bengay® or HEET®. It is also the active ingredient in oil of wintergreen.

In order to estimate the toxicity of certain non-aspirin salicylates, they are converted to an aspirin equivalent. For example, 1 mL of oil of wintergreen, which is 98% methyl salicylate is equivalent to 1,400 mg of aspirin.

The range of salicylate toxicity between cats and dogs varies greatly. Cats are more susceptible to toxicosis. Toxicity is possible in cats with acute oral ingestions greater than 30 mg/kg aspirin. Most healthy dogs will be able to tolerate acute oral doses of ASA less than 75–100 mg/kg without significant complication and can be managed at home. However, the induction of early emesis is indicated. However, chronic doses of aspirin from 15–35 mg/kg of ASA BID–TID have lead to submucosal gastric hemorrhage and gastric erosion within five to six days. Dogs acutely ingesting between 100–300 mg/kg of ASA should be evaluated by a veterinarian and supportive therapy instituted. Doses over 300 mg/kg of ASA warrant full and aggressive treatment. Ingestions of 400–500 mg/kg of ASA or greater carry a poor prognosis. In addition to oral dosing, topical application of salicylate creams will result in systemic absorption. However, overdoses from topical exposure would not be expected unless large quantities were used chronically.

Signs of toxicity appear hours to days post exposure. GI irritation is the most common sign of salicylate exposure while depression, vomiting, gastric erosion/ulceration/GI hemorrhage are other common effects. Additionally, hyperthermia, collapse, extreme weakness, tremors, seizures, bone marrow suppression, and cerebral edema may also occur. In severe cases, respiratory alkalosis may be noted soon after exposure and is followed by significant metabolic acidosis with an increased anion gap. Finally, due to platelet inhibition and reduced production of prostaglandin, adverse coagulation and renal effects may be noted. In cats, salicylate associated hepatitis has been reported as excessively high doses.

Treatment will vary from simple decontamination to aggressive life-support measures. Emesis or gastric lavage may be indicated, followed by activated charcoal. A course of gastrointestinal protectants including antacids, sulcralfate and misoprostil are needed for 10–14 days. If ulcerations are present, antibiotic treatment, analgesia, and blood transfusions may be needed. Baseline chemistry values, complete blood counts, and arterial or venous blood gasses are recommended. Additional supportive care such as intravenous fluids (forcing diuresis when necessary), the frequent monitoring of body temperature, and thermal support may be warranted, depending on the dose ingested. Seizures may be treated with diazepam. Sodium bicarbonate may be needed for acidemia.

5-Fluorouracil or 5-FU

Fluorouracil, also referred to as 5-FU, is an antineoplastic agent commonly found in creams prescribed for the treatment of human actinic keratosis and superficial basal cell carcinomas. Common topical preparations have a 0.5–5% concentration. Topical 5-FU creams have, historically, been used for the treatment of feline cutaneous tumors such as squamous cell carcinomas. However, this practice is no longer recommended as both severe toxicity and death have been reported following "routine" use in cats.

5-FU is a fluorinated pyrimidine antimetabolite that substitutes for the uracil nucleotide. Ultimately, it interferes with the synthesis and processing of DNA and RNA respectively. The ultimate result is programmed cell death. In healthy animals, the hematopoetic and epithelial cells (specifically the intestinal crypt cells) are most profoundly affected as they are the most rapidly dividing.

The most common exposure of cats and dogs to this product is via accidental oral exposure after chewing into a tube of the product. These preparations have an extremely narrow margin of safety and most ingestions must be considered medical emergencies. Cats are quite sensitive to the effects of 5-FU and even a few licks of the product may cause life-threatening toxicity. In dogs, the minimum reported

toxic dose following oral exposure is 6 mg/kg followed by a minimum reported lethal dose of 20 mg/kg. To date, the largest survived ingestion in a dog is 46 mg/kg of 5-FU.

The onset of clinical signs is very rapid, beginning 1–5 hours after ingestion. Because of the rapid onset of toxicity, the induction of emesis by the pet owner is not often recommended. Activated charcoal is recommended following gastric emptying. The most common signs of toxicity include rapid onset vomiting, death, and seizures and tremors that are often poorly responsive to diazepam. Additional manifestations of 5-FU toxicity include weakness, anorexia, abdominal pain, mucositis, diarrhea, GI erosions and ulceration, cerebellar ataxia, dose-dependent myelosuppression, cardiovascular collapse, and myocardial ischemia.

Treatment of toxicity must be aggressive. If seizures are not responsive to diazepam, other sedatives such as barbiturates, propofol, or gas anesthetics may be used. Intravenous fluids, blood or plasma transfusions, thermal support, gastrointestinal protectants, analgesics, and broad spectrum antibiotics may all be warranted. Laboratory evaluation should include frequent monitoring of chemistry profiles, complete blood counts, and coagulation profiles. Expect 2–3 weeks for cell lines to normalize.

CALCIPOTRIENE

Calcipotriene is a vitamin D analogue commonly used for the treatment of human psoriasis. Common brand names include Dovonex® and Taclonex ®. Toxicity from calcipotriene results in life-threatening hypercalcemia and hyperphosphatemia leading to dystrophic mineralization and subsequent renal failure. Death from cardiac failure secondary to hypercalcemia may also occur but is less likely.

The minimum acute toxic dose in dogs is 37 mcg/kg. This same dose has not been reported in cats but it is well established that they are more sensitive to the effects of calcipotriene than dogs are.

Signs of toxicity as well as electrolyte abnormalities typically begin only a few hours after ingestion. Signs include PU/PD, anorexia, vomiting, lethargy, melena, frank bloody diarrhea, hematuria, and death. While the renal system is often most acutely affected, eventually the cardiac, pulmonary, GI and CNS systems may be as well.

Treatment is focused on hypercalcemia and includes the frequent monitoring of electrolyte levels, especially calcium and phosphorus. It is helpful to note that, when checking electrolyte levels, hyperphosphatemia typically begins prior to hypercalcemia (which may take 24–36 hours to develop). In addition to standard treatment for hypercalcemia (IV fluids, prednisone, furosemide, saline diuresis, etc.) bisphosphonates such as pamidronate may be helpful (1.3–2 mg/kg IV diluted in saline over 2 hours; repeat in 3–7 days if needed).

PYRETHRINS AND PYRETHROIDS

Pyrethrins and their synthetic derivative, pyrethroids, are commonly found in premise and topical insecticides (i.e., permethrin, cyphenothrin, bifenthrin, cyhalothrin, etc). The diluted amount found in premise sprays and topical flea sprays and shampoos is typically <1%. Toxicity from exposure to these products is highly unlikely.

Cats are significantly more sensitive to pyrethrins than dogs. While a precise toxic dose for cats is not well established, products containing greater than a 5–10% concentration of pyrethrins may lead to systemic toxicity. The application of canine spot-on pyrethrin/pyrethroid based insecticides (typically ~40% concentration) to cats is the primary cause of feline pyrethrin toxicity. Cats that groom dogs following recent spot-on applications are also at high risk for toxicity. Dogs are rarely at risk for systemic toxicity from routine or accidental exposure to pyrethrins. Dogs are more likely to suffer a dermal paresthesia reaction secondary to a concentrated spot-on product.

Signs of systemic toxicity include hypersalivation, vomiting, hyperexcitability, twitches, tremors, dyspnea, weakness, disorientation, and seizures. Tremors are extremely responsive to injectable methocarbamol (give to effect) and less responsive to benzodiazepines. Seizures may be controlled with phenobarbital or general gas anesthesia. Dermal decontamination is crucial but should be performed after stabilization. Supportive care including the monitoring and maintenance of hydration, body temperature, and blood glucose levels are necessary. Signs may persist for 1–4 days, depending on the animal. The prognosis is excellent with aggressive treatment.

Paresthesia is manifested by scratching at or rubbing the pyrethrin application site, chewing on the feet or extremities, hiding, running frantically, and/or exhibiting nervous behavior. Because this is not an inflammatory reaction, redness and erythema are not present (unless secondary to self-trauma). Treatment is focused on decontamination with a de-greasing shampoo or hand-dishwashing detergent and the application of Vitamin E oil directly to the spot-on application site. Vitamin E oil may be re-dosed until no longer needed (typically 1–3 days). Other supports such as cool baths and cool compresses are helpful.

REFERENCES

1. Bischoff K, Guale F. Australian tea tree (*Melaleuca alternifolia*) oil poisoning in three purebred cats. *J Vet Diagn Invest* 10:208, 1988
2. Dorman DC, Coddington KA, Richardson RC. 5-fluorouracil toxicosis in the dog. *J Vet Intern Med* 4:254, 1990
3. Franke FE, Thomas JE. A note on the minimal fatal dose of nicotine for unanesthetized dogs. *Proc Soc Exp Biol Med* 29:1177–, 1932
4. Fry MM, Forman MA. 5-fluorouracil toxicity with severe bone marrow suppression in a dog. *Vet Hum Toxicol* 46:178, 2004
5. Larson PS, Silvette HB. *Tobacco: experimental and clinical studies.* Supplement; Williams and Wilkins, Baltimore, 1968
6. Pet Poison Helpline™ Database, Bloomington, MN. Accessed May 15, 2008.
7. Plumb DC. *Plumb's Veterinary Drug Handbook*. 5th ed. Blackwell, Ames, 2005
8. Plumlee KH. Nicotine. p. 898. In Peterson ME and Talcott PA (eds): *Small Animal Toxicology*. 2nd ed. Saunders Elsevier, St. Louis, 2006
9. Reimer ME, Johnston SA, Leib MS, *et al*. The gastroduodenal effects of buffered aspirin, carprofen, and etodolac in healthy dogs. *J Vet Intern Med* 13:472, 1999
10. Roberts J, Powell LL. Accidental 5-fluorouracil exposure in a dog. *J Vet Emerg Crit Care* 11:281, 2001
11. Sennello KA, Leib MS. Effects of deracoxib or buffered aspirin on the gastric mucosa of healthy dogs. *J Vet Intern Med* 20:1291, 2006
12. Talcott PA. Nonsteroidal antiinflammatories. 902. In Peterson ME and Talcott PA (eds): *Small Animal Toxicology.* 2nd ed. Saunders Elsevier, St. Louis, 2006
13. Villar D, Knight MJ, Hansen SR, *et al*. Toxicity of melaleuca oil and related essential oils applied topically on dogs and cats. *Vet Hum Toxicol* 36:139, 1994
14. Welch SL. Oral toxicity of topical preparations. 443. In Poppenga RH and Volmer PA (eds): *The Veterinary Clinics of North America, Small Animal Practice: Toxicology*. W. B. Saunders, Philadelphia, 2002