TOPICAL TOXINS – ONE TUBE CAN KILL

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Many people assume that topical medications are benign, as they can be "smeared" on the skin; however, certain types can be quite toxic – even deadly - to our veterinary patients. This lecture will review the most common topical toxins seen, the mechanism of action, the clinical toxicosis associated with exposure, and overall treatment.

ZINC OXIDE

Topical zinc oxide cream is often used as a protectant against irritants (e.g., diaper rash cream), as a treatment for skin irritation, or as a sun protectant (e.g., sunscreen). Zinc oxide can be found over-the-counter (OTC) in concentrations ranging from 5-61%. Common brands include Desitin®, Boudreaux's Baby Butt Balm®, and generic pharmacy brands. When ingested by dogs, minor toxicosis results. Severe toxicosis is rare, but reported with sub-acute, massive ingestions. With acute ingestion, gastrointestinal signs (e.g., vomiting, diarrhea)[1] may be seen, as zinc is a potent emetic agent. This often assists in self-decontamination of the product, preventing further toxicosis. While this topical cream contains zinc, heavy metal toxicosis from elemental zinc is rare, unless ingested in massive (or chronic) amounts. If a large amount of the plastic tubing was ingested, the potential for foreign body obstruction (FBO) exists. In general, most of these poisonings can be treated on an outpatient basis. Treatment includes symptomatic supportive care, including anti-emetics, fluid therapy [subcutaneous (SQ) or intravenous (IV), if severe], a bland diet, and potentially anti-diarrheals.

5-FLUOROURACIL (5-FU)

One of the most dangerous topical toxins to be aware of is 5-fluorouracil (5-FU), which is a prescription anti-neoplastic medication used topically for humans with superficial basal cell carcinoma or actinic keratosis. Brand names include Efudex®, Carac®, Adrucil®, and Fluoroplex®, and range in concentration from 0.5-5%. These drugs work by inhibiting DNA and RNA synthesis and production, resulting in programmed cell death.[1,2]

In veterinary medicine, the use of IV 5-FU is still used as a chemotherapeutic agent in dogs; however, it is not recommended for use in cats. Decades ago, topical 5-FU was used for the treatment of squamous cell carcinoma in cats; however, due to severe toxicosis and death associated with its use, the topical chemotherapeutic was no longer considered safe. When ingested by dogs or cats, even tiny amounts can be very toxic, resulting in acute gastrointestinal (GI) signs, central nervous system (CNS) signs, and bone marrow suppression.[1,2] In dogs, the lowest reported toxic dose following oral exposure is 6 mg/kg.[1,2] In dogs, the minimal reported lethal dose is 20 mg/kg; that said, the largest survived ingestion in a dog was 46 mg/kg of 5-FU.[1,2] 5-FU is rapidly absorbed from the gastrointestinal tract (GIT), and clinical signs can often be seen within 30 minutes up to 6 hours; death has been reported as early as 7 hours.[1,2] The prognosis with 5-FU ingestion is grave in cats and guarded in dogs (with a reported survival in dogs of approximately 25%).

Clinical signs include acute nausea, vomiting, hemorrhagic diarrhea, abdominal pain, sloughing of the GIT, ataxia, severe seizures (that are often non-responsive to traditional anticonvulsants like diazepam or phenobarbital), 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 dysfunction syndrome (MODS) can be seen. Typically, decontamination is not effective due to rapid absorption of the drug from the stomach, and due to rapid onset of clinical signs. Treatment is supportive and includes anti-convulsant therapy (e.g., diazepam, phenobarbital, propofol, gas anesthesia), anti-emetic therapy, IV fluids to maintain perfusion to both the GI 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., complete blood count (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. Once a patient has survived the acute toxicosis of 5-FU, sub-chronic monitoring of bone marrow function is necessary. 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.[1,2]

CORTICOSTEROID OINTMENTS

Topical steroid creams or ointments, which generally contain common products like betamethasone, hydrocortisone, triamcinolone, etc., have a wide margin of safety.[1] When ingested by dogs or cats, mild signs of gastrointestinal distress (e.g., vomiting, diarrhea) may be seen secondary to the petroleum-based carrier.[1] Clinical signs of polyuria, polydipsia, and polyphagia may be seen acutely; however, these signs are self-limiting. When ingested, veterinary treatment is rarely required unless clinical signs are significant.

ANTIBIOTIC OINTMENTS

Topical antibiotic ointments – both human and veterinary – often contain a mixture of neomycin sulfate, polymyxin sulfate, and bacitracin.[1] When ingested by dogs or cats, mild signs of gastrointestinal distress (e.g., vomiting, diarrhea) may be seen secondary to the petroleum-based carrier. When ingested, veterinary treatment is rarely required unless clinical signs are significant.

CALCIPOTRIENE

Another dangerous topical toxin is calcipotriene. This Vitamin D analogue is commonly used for the treatment of human psoriasis, and is available under brand names like Taclonex® and Dovonex®. Ingestion of these topical creams can be deadly – and costly – to pets, as it results in severe hypercalcemia and hyperphosphatemia, with secondary mineralization of the kidneys and soft tissues. This dystrophic mineralization can result in severe acute renal failure (ARF) and potentially chronic renal failure (CRF).[3] Death from cardiac failure secondary to hypercalcemia may also occur, but is less common.[1,3]

In dogs, the minimal acute toxic dose reported is 37 mcg/kg.[1,3] While an established toxic dose is not reported in cats, cats seem to be more sensitive to the effects of calcipotriene than dogs. Clinical signs seen with calcipotriene toxicosis may not be seen for 1-3 days, until the patient has already developed clinical signs of ARF. Clinical signs and clinicopathologic findings include pu/pd, weakness, lethargy, anorexia, vomiting, generalized malaise, uremic halitosis, dehydration, hypercalcemia, hyperphosphatemia, and azotemia.[1,3] Treatment includes decontamination (e.g., emesis induction, if appropriate), the aggressive use of IV fluid therapy to promote calciuresis (e.g., 0.9% NaCl), calcium monitoring, and the use of medications to increase calciuresis (e.g., prednisone, furosemide) and prevent hypercalcemia (e.g., pamidronate, calcitonin). As calcipotriene undergoes enterohepatic recirculation, multiple doses of activated charcoal (without cathartic) every 6 hours X 24 hours should be administered. Treatment for calcipotriene toxicosis is often expensive, and requires hospitalization for an extended period of time (e.g., 2-7 days). Most patients are continued on oral furosemide and prednisone for weeks, following discharge from the hospital. Frequent monitoring of renal function and electrolytes is imperative. Calcium, phosphorous, BUN, creatinine, and ionized calcium should be evaluated every 12-24 hours while hospitalized, and then every 2-5 days thereafter for the next 2-4 weeks. This will allow one to assess the ability to titrate the prednisone and furosemide therapy, and to ensure that the patient does not develop secondary ARF or CRF. Even with aggressive treatment, CRF may be a secondary sequela.

TEA TREE (MELALEUCA) OIL

Tea tree oil, also known as melaleuca oil, is an essential oil produced from the Australian tea tree (*Melaleuca alternifolia*) plant.[4] Tea tree oil is known for its antifungal and antibacterial properties, and possibly for its antipruritic, anti-inflammatory, and antiparasitic effects.[4] Tea tree oil is often found in varying concentrations (from <1% to 100%) in shampoos, conditioners, body lotions, face washes, toothpastes, insect repellents, holistic oils, etc.[4] While its use is generally considered safe for humans, toxicosis has been reported in dogs and cats when the concentrated (100%) oil is used topically by well-intentioned pet owners who are seeking a “holistic” or “natural remedy.” As little as 7 drops of 100% oil has resulted in toxicosis, and applications of 10-20 mls of 100% oil have resulted in toxicosis and death in both dogs and cats.[1,4] Clinical signs can be seen within 1-2 hours after application, and include mild to

moderate hypothermia, weakness, CNS depression, ataxia, rear limb weakness, and generalized muscle tremors.[1,4] Rarely, coma, increased liver enzyme elevation, dermal or oral irritation, or cardiorespiratory effects may be seen.[1,4] Signs slowly resolve over 2-4 days.[1,4] Treatment includes dermal decontamination with a degreasing, liquid dish soap (e.g., Palmolive, Dawn) to remove the excess oil and reduce dermal absorption. If orally ingested, emesis induction is typically not recommended, as rapid GI absorption occurs and risk of aspiration of the oil exists. As tea tree oil undergoes enterohepatic recirculation, the use of multiple doses of activated charcoal (without a cathartic) may be warranted provided the patient has an appropriate gag reflex and is not at risk for aspiration. In severely affected patients, the use of IV fluids is warranted to maintain hydration and tissue perfusion. Temperature support may be necessary, along with nursing care. Baseline biochemistry testing is warranted; liver enzymes should be rechecked q 5-7 days until clinical signs resolve or liver enzymes return to normal. The use of hepatoprotectants (e.g., SAMe) is warranted if indicated based on biochemical testing.[4] Overall, treatment is symptomatic and supportive, and the prognosis is fair provided hepatic injury or severe clinical signs are not seen.

PYRETHRINS AND PYRETHROIDS

Pyrethrins are a class of drugs derived from the *Chrysanthemum* flower/plant, while pyrethroids are synthetic derivatives.[1,5] These products typically come in concentrations ranging from <1% up to 50-60%, and are used as common household insecticides, premise sprays, topical spot-on flea and tick ointments, and pet shampoos. Toxicity from low concentration products (<1%) is very rare.[1]

As cats have an altered glucuronidation pathway, they cannot metabolize pyrethins/pyrethroids and hence, are significantly more sensitive to this class of drugs as compared to dogs. In general, products containing > 5-10% may result in systemic toxicity in cats.[1] One of the most common sources of toxicosis in cats is the inappropriate application of canine-specific spot-on pyrethrin/pyrethroid products (which typically range from 40-55%). Also, cats may be exposed to toxicosis by licking or grooming the product off a dog that had recent topical spot-on application.[1]

In cats, systemic toxicosis results in clinical signs of hypersalivation, tremoring, vomiting, hyperexcitability, seizures, tachypnea, weakness, etc.[1] Treatment includes the use of a centrally-acting muscle relaxant (e.g., methocarbamol, 55-220 mg/kg IV, PRN) to stop the tremors. These tremors are generally poorly responsive to benzodiazepines, so the use of methocarbamol is preferred. The use of anticonvulsants (e.g., phenobarbital, gas inhalation, etc.) is warranted for grand mal seizures. Once the patient has been stabilized and sedated, the use of dermal decontamination (e.g., degreasing, liquid dish soap) is warranted to completely remove the product. Supportive care (including temperature regulation, fluid therapy administration, blood pressure monitoring, etc.) is also indicated. Typically, clinical signs resolve after 1-3 days.

In dogs, systemic toxicosis is not generally seen; rather, a dermal paresthesia reaction may be seen. This “tingling” sensation to the area of application may result in clinical signs of pruritis, frantic rubbing of the application site, chewing on the feet or extremities (if the product was spread to the feet by itching at the site of application), hiding, nervous behavior, panting, etc.[1] Typically, parasthesia is not considered an “allergic” or inflammatory reaction; therefore, the use of diphenhydramine and steroids is not typically necessary. However, secondary signs of inflammation (e.g., redness, warmth, etc.) may be present secondary to self-trauma. Treatment includes dermal decontamination (e.g., degreasing liquid dish soap), application of cool compresses to the area, prevention of further mutilation to the site (e.g., e-collar, t-shirt), and application of topical Vitamin E oil directly to affected area.[1] Typically, in dogs, signs resolve rapidly once the product is bathed off.

CONCLUSION

Topical medications – both OTC and prescription – are readily available throughout the household. Veterinary professionals should be aware of the dangers of these topical toxins. The use of judicious and appropriate decontamination and aggressive symptomatic and supportive care is warranted, when indicated.

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