Human Medications and other Seasonal Toxins

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Acetaminophen

Acetaminophen (Tylenol®, non-aspirin pain reliever, APAP) is a synthetic non-opiate derivative of p-aminophenol. It is available in tablets, liquid preparations, and long-acting compounds. Tablet strengths vary from 80 to 650 mg. Liquids are available in 160 mg/5 ml, 100 mg/ml, and 120 mg/2.5 ml. APAP's exact mechanism of action is unknown but it is believed to block production of prostaglandins from arachidonic acid by inhibiting COX-3. APAP 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. 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, hyperventilation, icterus, vomiting, methemoglobinemia, hypothermia, facial or paw edema, death, cyanosis, dyspnea, and hepatic necrosis. 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. Hepatotoxicity has been reported in dogs at 100 mg/kg and 200 mg/kg caused clinical methemoglobinemia in 3 out of 4 dogs. Therapeutic doses have resulted in KCS 72 hours after ingestion. Cats develop clinical signs at doses > 40 mg/kg. No dose is safe in cats since they are deficient in glucuronyl transferase. Ferrets are considered to be as sensitive as cats.

Early decontamination is most beneficial. Emesis can be performed in the asymptomatic animal, unless contraindicated. 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. Serum albumin concentrations decrease significantly after 36 hours and continue to decrease during liver failure, providing a true index of liver function.

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 or can be oxidized to organic sulfate which provides 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. With ingestion of

massive quantities some authors suggest using 280 mg/kg for a loading dose and continuing treatment for 12 to 17 doses. 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. NAC is now 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 transfusions or oxyglobin may be necessary to increase oxygen carrying capacity.

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. Cimetidine is an inhibitor of cytochrome p-450 oxidation system but takes several days to become effective. Cimetidine should not be used in cats as it blocks an important metabolic pathway needed for detoxification. 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.

Ibuprofen

Ibuprofen (Motrin®, Advil®, Midol®, etc.) is a nonsteroidal anti-inflammatory agent. It is available over the counter in 50, 100, 200 mg tablets and 100 mg/5 ml suspension. Prescription strength tablets are 400, 600, and 800 mg. Ibuprofen inhibits prostaglandin synthesis by blocking the conversion of arachidonic acid to various prostaglandins. Ibuprofen decreases secretion of the protective mucous layer in the stomach and small intestine and causes vasoconstriction in gastric mucosa. Ibuprofen inhibits renal blood flow, glomerular filtration rate, tubular ion transport, renin release and water homeostasis. Ibuprofen may also affect platelet aggregation and possibly hepatic function. Serious hepatotoxicosis is not a common problem with ibuprofen.

Absorption of ibuprofen is rapid (0.1 to 1.5 h). Plasma half life in the dog has been reported to be 2-2.5 hours, but the elimination half life is considerably longer. Ibuprofen is metabolized in the liver and undergoes significant enterohepatic recirculation before being excreted in the urine. Geriatric animals and neonates, as well as animals with acute renal insufficiency, liver disease, and hypoalbuminemia are at higher risk of toxicosis. Administration of ibuprofen in combination with glucocorticoids, salicylates, or other NSAIDS could potentiate the adverse effects of these drugs.

Ibuprofen has a narrow margin of safety. Even at the therapeutic dog dosage of 5 mg/kg, ibuprofen may cause gastric ulcers and perforations with chronic use. In dogs, an acute exposure of 50-125 mg/kg can result in gastrointestinal signs (vomiting, diarrhea, abdominal pain, anorexia), > 175 mg/kg can result in more severe GI signs (hematemesis, melena) plus renal damage (PU/PD, oliguria, uremia). Doses of > 400 mg/kg in the dog result in GI, renal, and CNS signs (seizure, ataxia, coma). Cats are thought to be twice as sensitive to ibuprofen's toxic effects as dogs due to their limited glucuronyl-conjugating capacity. Ferrets that ingest ibuprofen are at high risk for CNS depression and coma, with or without GI upset.

The onset of GI upset is generally within the first 2-6 hours after ingestion, with GI hemorrhage and ulceration occurring 12 hours to 4 days post ingestion. Renal failure often occurs within the first 12 hours after massive exposure to an NSAID but may be delayed for 3-5 days.

Emesis can be performed in the asymptomatic animal. Activated charcoal adsorbs ibuprofen and may need to be repeated (enterohepatic recirculation). A cathartic should also be used, unless the animal is dehydrated or has diarrhea. GI protectants are very important. A combination of misoprostal, H2 blockers, sucralfate and omeprazole can be used to manage and/or prevent gastric ulcers. Animals should be started on IV fluids at twice maintenance for 48 hours if renal failure is expected. Monitor BUN, creatinine, and urine specific gravity (baseline level, 24, 48, and 72 h). Acid-base disturbances are rare and usually transient. Peritoneal dialysis may be necessary if unresponsive oliguric or anuric renal failure develops.

Fluids, whole blood, inotropic agents, and electrolytes should be given to control hypotension and hemorrhage, maintain renal function, and correct electrolyte abnormalities. Assisted ventilation and supplemental oxygen may be required if animal is comatose. Seizures should be treated with diazepam.

Prognosis is good if the animal is treated promptly and appropriately. Gastrointestinal ulceration usually responds to therapy. Acute renal insufficiency resulting from ibuprofen administration has been considered reversible, but development of papillary necrosis is generally considered irreversible.

Other NSAIDs

Clinical signs and treatment are similar to ibuprofen. However, tolerance of NSAIDS varies considerably between species and for most NSAIDs the minimum toxic or lethal dose is not clearly established. Hepatotoxicity can be seen with any NSAID and is thought to be an immune mediated reaction. Most cases are reversible with supportive care.

Naproxen (Naprosyn®, Aleve®): OTC formulations of naproxen include 220, 250, 275, 375, 500 and 550 mg pills and 125 mg/tsp suspension. Half life in the dog is 74 hours, as the drug undergoes extensive enterohepatic recirculation. Ulcerative gastritis is possible in dogs at 5 mg/kg/day for 7 days and doses of > 25 mg/kg can cause acute renal failure. Due to the prolonged half life, fluids need to be continued for at least 72 hours and GI protectants for 10-14 days.

Celecoxib (Celebrex®), valdecoxib (Bextra®), rofecoxib (Vioxx®) and ***deracoxib (Deramaxx®)*** are COX-2 inhibitors. Dogs do not have the cardiac problems seen in humans as dogs do not develop atherosclerosis.

Decongestants

Pseudoephedrine and phenylephrine are common components of many cold and allergy medications. Pharmacologically they are sympathomimetic alkaloids. The alkaloids stimulate alpha- and beta-adrenergic receptors, causing the release of endogenous catecholamines at synapses in the brain and heart. This stimulation causes peripheral vasoconstriction and cardiac stimulation resulting in hypertension, tachycardia, ataxia, restlessness, tremors, and seizures. Because signs can occur as early as 15-30 minutes of ingestion, decontamination at home is often not recommended. With ingestions of extended release forms, signs may not be seen for several hours. Asymptomatic animals may have emesis induced and activated charcoal administered. Fluid therapy is important to enhance elimination and maintain CV stability. Agitation, hyperactivity, and tremors tend to respond best to phenothiazines. For acepromazine and chlorpromazine, start at the low end of the dosage range and increase as needed. Diazepam can

worsen dysphoria and is not recommended. Because part of the syndrome is related to serotonin excess, cyproheptadine (1.1 mg/kg 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, propranolol may be used. Signs may persist up to 48-72 hrs in severe cases.

Dextromethorphan (DMX)

Dextromethorphan is used as a cough suppressant. It is also commonly abused by teenagers. Dextromethorphan can cause both serotonin syndrome and dystonic reaction by blocking dopamine activity. DMX is available as both tablets and liquid. It is found as a single agent and in combination with other cold medications. In most cases, signs are seen within 30 minutes to 4 hours and recovery occurs within 24 to 36 hours. In animal cases, facial swelling is the most common reaction (about 30% of cases). Initial lethargy and ataxia can be followed by agitation, tachycardia, hyperactivity, mydriasis, tremors, hyperthermia, disorientation, hyperesthesia, and seizures. Treatment includes confinement and minimizing sensory stimuli. Dystonic reactions can be treated with diphenhydramine. Diazepam is indicated for tremors and seizures. Phenothiazines and cyproheptadine can be used to treat serotonin syndrome. Good prognosis with treatment.

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.

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 owner. The animal may be ataxic and disoriented. Coma and death may occur during this stage, or may appear to partially or fully recover over 3-6 hours. By 6-12 hours, the neurologic status may again deteriorate due to development of severe metabolic acidosis from ethylene glycol metabolites. Marked CNS depression, stupor or coma can occur and 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)*. 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. Any suspected oral exposure of an animal 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. Cats are much more sensitive than dogs to ethylene glycol.

There are two available patient side ethylene glycol tests: VetSpec (Catachem) and Kacey. The VetSpec 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 and 50 mg/dl in dogs 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. Emesis and activated charcoal are somewhat controversial, as aliphatic alcohols are not thought to be well adsorbed by charcoal. Animals 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 fluid therapy is the cornerstone of treatment. 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 animals 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. 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 in cats 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 the animal is 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 animals may fully recover or may have residual renal insufficiency requiring lifetime maintenance. The presence of oliguria/anuria indicates a grave prognosis.

Ice Melts

Many brands of sidewalk ice melts are on the market. The most common ingredients in these ice melts are sodium chloride, potassium chloride, magnesium chloride, calcium chloride,

calcium carbonate, and calcium magnesium acetate. A few ice melts contain urea. Cats may be exposed by walking on the ice melts themselves or by ingesting granules brought inside on the shoes of the owner's.
Ingestion of urea is not a toxicity issue in non-ruminants. Ingestion of sodium, potassium, calcium and magnesium salts can lead to vomiting and electrolyte abnormalities. Monitor electrolyte levels and treat with appropriate fluid therapy.

Poinsetta (*Euphorbia pulcherrima*)

Poinsettas are overrated as a toxic plant. They do contain diterpenoid euphorbol esters in their sap which can cause vomiting.

Amaryllis

Common bulb plants include tulips,, daffodils, narcissus, amaryllis and hyacinths. All parts of the plant are toxic, but the bulb is the most toxic. Ingestion of the flower or stem can cause vomiting. Ingestion of the bulbs can cause hemorrhagic gastroenteritis and neurologic signs.

Christmas Cactus

The Christmas cactus (*Schlumbergera truncate*) is considered to be non-toxic. Ingestion may cause mild gastrointestinal upset.

Mistletoe

Most ingestions involve American mistletoe (*Phoradendron* spp.). Mistletoe contains lectins, but ingestion of a few leaves or berries will generally cause just a mild gastritis. If purchased in a store, the berries frequently have been removed and replaced with plastic "berries" which can be a foreign body. Large ingestions may require decontamination and cardiovascular monitoring.

American Holly

American holly (*Ilex opaca*)is a member of the Aquifoliaceae family. All parts of the holly plant are considered to contain potentially toxic compounds, including methylxanthines, saponins, and ilicin. True toxicoses not generally expected in cats and dogs. Most ingestions cause gastrointestinal irritation and depression. Recent ingestions can usually be managed with dilution and monitoring at home.

***Kalanchoe sp.* – devil's backbone, mother of millions, Mexican hat plant**

This is a common household plant, especially around the holidays. This plant contains cardiac glycosides, but most dogs and cats only develop GI signs.

Anticoagulant Rodenticides

Anticoagulants in use as rodenticides today are almost all second-generation derivatives of either warfarin or indane 1,3-dione. They are active in the liver where they inhibit the activity of vitamin K epoxide reductase, which converts the vitamin K epoxide to the active reduced form. This reduced vitamin K is crucial to activation of clotting factors II, VII, IX, AND X.

The concentration of active chemical in an anticoagulant bait can range from 0.002%-1%, but the vast majority are 0.005%. Container sizes vary, so having the package with label is very

useful in estimating exposure. Doses need to be calculated in mg active chemical/kg BWT. If concentration is 0.005%, each gram of bait has 0.05 mg of the active component. When there is uncertainty about the amount consumed, use the amount potentially available to make calculations.

At the ASPCA Animal Poison Control Center we use an exposure of 0.02 mg/kg BWT as the dose that triggers treatment and evaluation. If ingestion was witnessed or a window of opportunity places it within a couple hours, we generally start with inducing emesis. If little or no bait is recovered, administration of activated charcoal is next. If the ingested dose is over 0.02 mg/kg and there has been no decontamination, you can simply institute Vitamin K1 without initial testing. We commonly recommend this approach with young animals, as they have smaller stores of clotting factors initially.

Because the body has several day's worth of active Vitamin K stored in the liver (the site of the re-activation activity), there is a delayed onset of effect on blood clotting after ingestion of an anticoagulant. Factor VII has the shortest half-life, so we can get the earliest valid estimate of effect by checking the prothrombin time (PT). The PT is expected to elevate within 24-48 hours post ingestion. A normal PT at 48-72 hours, with no elevation from baseline, is good evidence that there is no need for Vitamin K_1 therapy. If the dose is over 10% of the LD50 in a species and there has been no decontamination, you may just recommend the Vitamin K with PT 48 hours after stopping the meds.

When K_1 therapy is needed, target dose is 3-5 mg/kg. If there has been a large ingestion or if PT is very high, it is a good idea to repeat the PT after several days. If it is not yet in the normal range, you may need to increase the dose. Repeating the PT 48 hours after the final dose of K1 can determine that treatment has been sufficient.

A witnessed or evidenced exposure is manageable, and the goal is to prevent any bleeding episodes. When the exposure was not witnessed or suspected, diagnosis and treatment are more challenging. Early signs of anticoagulant toxicosis are vague, and depend on the site of a bleed. You may see lethargy, a soft, non-productive cough, intermittent lameness, mild anemia, or even sudden collapse. Frequently there is no obvious hemorrhage. Petechiae and echymoses are more often seen later in the course of illness, after the platelet numbers have been depleted in smaller bleeds. Diagnosis is based on signs, history of possible exposure, and coagulation studies. The PT will be elevated at 24-48 hours.

Therapy depends on the severity of signs shown. Vitamin K1 is started at 3-5 mg/kg BWT, using the higher doses in smaller animals and more severely affected animals. Horses should get about 2 mg/kg, per Beasley (pp914-915, 1997 notes). There is no real need to give via injection unless the animal is not eating. If injecting, use the smallest needle possible and give IM or SQ, not IV. Giving Vitamin K1 via IV significantly increases the risk of an anaphylactic reaction. The dose can be divided bid and given with a small amount of fatty food to aid absorption. If necessary, the injectible form can be given by mouth (very small animal, difficult to pill, capsules not available)

If there has been significant blood loss, these animals may be good candidates for whole blood transfusions, fresh frozen plasma (to replace clotting factors quickly) or Oxyglobin™. Minimize invasive procedures as much as possible to avoid starting new bleeds. If there is a hemothorax with dyspnea, thoracocentesis can be a lifesaver. If a hemothorax is present but there is no dyspnea, continue to monitor, the blood may be resorbed during the course of therapy.

Minimize physical activity throughout therapy, but most stringently during the first 1-2 weeks, until clotting factors have been restored to normal by the Vitamin K. Even mild exercise can initiate a bleeding event when there is a defect in the clotting cascade.

Bromethalin

Bromethalin is a neurotoxin that uncouples oxidative phosphorylation in CNS mitochondria. This results in lack of adequate ATP concentration and insufficient energy for maintaining Na^+-K^+ ion channel pumps. Loss of pump activity results in cerebral and spinal cord edema and a demyelination injury to long nerves. The usual concentration is 0.01% in both pelleted baits and in bait blocks

Bromethalin is rapidly absorbed from GI tract. Effects are mostly neurological, and can mimic a number of different disorders Minimal lethal dose of bait generally reported in dogs is 25 gm bait or 2.5 mg active ingredient/kg BWT. APCC data had documented deaths in dogs at doses as low as 0.96 mg/kg. Cats are far more sensitive to this agent than are dogs. For cats it is only 4.5 gm bait /kg BWT. As most packets are 21 grams, a single packet can be lethal to a 10-pound cat. Interestingly, the toxicity on a dose/kg basis in a bait formulation is much higher than reported based on toxicity studies in which the technical bromethalin was used.

Dogs seem to have both a low-dose and a high-dose syndrome. With lower doses signs may not appear for 72-96 hours, and include hind limb ataxia and paresis, decreased proprioception, loss of deep pain response, vocalizations, patella hyper-reflexia, CNS depression progressing to coma, vomiting, and fine muscle tremors. At or above the mean lethal dose, signs can begin within 12-24 hours and include severe tremors, hyperthermia, extreme hyperexcitability, running fits, hyperesthesia and seizures.

Treatment of clinical signs is directed to controlling cerebral edema, and is mostly frustrating and non-productive. Mannitol, corticosteroids and diazepam may be used. Animals with sub-lethal doses will require good nursing care and supplemental feedings.

Cholecalciferol

Cholecalciferol is a Vitamin D_3 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 iwalls of blood vessels. The elevated calcium also has a direct effect on kidney function, sometimes causing acute renal failure even without mineralizations.

Without an observed exposure, diagnosis can be challenging. Differentials for hypercalcemia must include the normal juvenile state, hypercalcemia of malignancy, a hypoadrenal condition, primary renal failure, primary hyperparathyroidism, and disuse osteoporosis.

Diagnosis of toxicosis is based on history of exposure, clinical signs, serum chemistries and urinalysis. Run baseline chemistries as soon as possible after a known exposure. Pursue GI decontamination if within several hours of ingestion, or if there is evidence of ingestion (chewed box) at unknown time but a still asymptomatic animal.

Treatment is aimed at lowering the serum calcium and phosphorus levels if the product of Ca X Phos is over 60, preventing a rise in these values if still normal, and stopping further calcium mobilization from the bones. IV normal saline at twice maintenance, prednisone and furosemide all enhance calciuria. Monitor serum calcium, phosphorus, BUN and creatinine daily to judge effectiveness of therapy. Especially with a young animal, don't wait for sign to begin to start treating. If calcium levels are rising despite calciuresis, best choice is pamidronate (Aredia™). Unlike salmon calcitonin, it needs to be given only once, with a repeat dose possibly at about 5-7 days. It acts at the level of the osteoclast and is deposited in the bone itself. Dose is 60-90 mg (about 1.3 mg/kg) mixed in 500-700 ml saline and given slowly over 2-4 hours. A drawback can be the expense, about $250-300/60 or 90 mg vial. The advantage is that it works quickly in a majority of dogs. We have also documented the use and rapid response in at least one cat.

Once the pamidronate has been administered, it is important to taper the initial treatments (prednisone, furosemide) and decrease the rate of fluid administration. Continue to monitor calcium, phosphorus, and kidney values during this time. End of therapy will be marked by a return to normal of kidney values and the decrease of calcium x phosphorus levels (in mg/dl) to less than 60.

Zinc Phosphide

Zinc phosphide is an old rodenticide posing as a new one. The dark gray powder in not soluble in water, is commonly sold as a 2%-5% bait, and may be in the form of a paste or tracking powder as well as a grain-based product. In the past several years an oat-based bait labeled for killing prairie voles has been marketed. There is evidently no way to identify this as bait, and not just as oats, once the product is removed from the bag; this has proved lethal to a number of horses.

The phosphide salts are unstable in an acid environment. At gastric pH they degrade rapidly to form phosphine gas. Phosphine gas, when inhaled, results in acute non-cardiogenic pulmonary edema. When absorbed systemically, it is thought to block cytochrome C oxidase, leading to formation of highly reactive oxygen compounds.It is these reactive compounds which cause most of the tissue injury, most severe damageis in tissues with the highest oxygen demand – brain, lungs, liver and kidney.

Lethal doses cattle, sheep, pigs, goats, dogs, and cats range between 20-50 mg/kg. For a 55 pound (25 kg) dog, that would be between 10 grams (0.35 ounce) and 25 grams (just under an ounce) of 5% bait. Severely poisoned animals may die in 3-5 hours. Those who survive longer that 48 hours have a pretty good chance.

Initial signs may vary by species, as well as by the dose. Onset of signs is normally between 15 minutes to 4 hours post ingestion. Vomiting, often with blood, is common. Dogs may show lateral recumbency with whole body tremors and salivation.

Other signs may include anorexia and lethargy. Rapid deep breathing may signal the onset of the pulmonary changes. Abdominal pain, ataxia, and weakness leading to recumbency may follow. Hyperesthesia and seizures may develop that resemble the signs of strychnine toxocosis.

Metabolic acidemia ensues. Other biochemical changes may include depressed serum calcium and magnesium. If there is survival beyond 48 hours an elevated blood urea is common. Hepatic enzymes may elevate after several days as well.
Hepatic and renal damage often may be detected 5-14 days later.

Initial decontamination is tempered by the wish to keep the stomach pH as high as possible to prevent the formation of phosphine gas. If there has been no spontaneous vomiting, it may be better to induce emesis with apomorphine rather than hydrogen peroxide. Giving food, commonly done in order to improve gastric emptying and the response to peroxide, will trigger release of gastric acid and increase the rate of production of phosphine. If you are going to perform gastric lavage, add an alkalizing component like a magnesium and aluminum hydroxide gel to your lavage liquid. Also consider mixing into your activated charcoal preparation.

Supportive care included IV fluids to maintain blood pressure renal perfusion, and gastroprotectants like carafate or kaopectate after decontamination is completed. Corticosteroids won't hurt. Seizures may respond to diazepam, or may require barbiturates or full anesthesia. Since the most severe injury is probably due to action of the oxygen radicals, use of an antioxidant may be useful – consider vitamin C or n-acetylcysteine.

Caution: Phosphine gas released from vomitus or stomach washings can cause significant illness in veterinary personnel assisting animal. Phosphine has been describes as having a spoiled fish or garlic odor. It is detectable at 1-3 ppm in air; maximum allowed in air in occupational situations is 0.3 ppm, so if you can smell it, you are being exposed to a concentration that can be harmful.

Chocolate

There are a wide variety of chocolate and cocoa products to which pets may be exposed, including candies, cakes, cookies, brownies, and cocoa bean mulches. Not surprisingly, the incidence of accidental chocolate exposures in pets occurs around holidays, especially Valentine's Day, Easter, Halloween and Christmas. The active (toxic) agents in chocolate are methylxanthines, specifically theobromine and caffeine. Methylxanthines stimulate the CNS, act on the kidney to stimulate diuresis, and increase the contractility of cardiac and skeletal muscle. The relative amounts of theobromine and caffeine will vary with the form of the chocolate.

Methylxanthine levels of various chocolates

Compound	Milligrams per ounce Theobromine	Caffeine
White Chocolate	0.25	0.85
Milk Chocolate	58	6
Semi-sweet Chocolate chips	138	22
Baker's Chocolate (unsweetened)	393	47
Dry cocoa powder	737	70

The LD_{50}'s for theobromine and caffeine are 100-300 mg/kg, but severe and life threatening clinical signs may be seen at levels far below these doses. Mild signs have been seen with theobromine levels of 20 mg/kg, severe signs have been seen at 40-50 mg/kg, and seizures have occurred at 60 mg/kg. Accordingly, less than 2 ounces of milk chocolate per kg is potentially lethal to dogs.

Clinical signs occur within 6-12 hours of ingestion. Initial signs include polydipsia, bloating, vomiting, diarrhea, and restlessness. Signs progress to hyperactivity, polyuria, ataxia, tremors, seizures, tachycardia, PVC's, tachypnea, cyanosis, hypertension, hyperthermia, and coma. Death is generally due to cardiac arrhythmias or respiratory failure. Hypokalemia may occur later in the course of the toxicosis. Because of the high fat content of many chocolate products, pancreatitis is a potential sequela.

Management of chocolate ingestion includes decontamination via emesis followed by gastric lavage. Because methylxanthines undergo enterohepatic recirculation, repeated doses of activated charcoal are usually of benefit in symptomatic animals. Intravenous fluids at twice maintenance levels will help maintain diuresis and enhance urinary excretion. Because caffeine can be reabsorbed from the bladder, placement of a urinary catheter is recommended. Cardiac status should be monitored via EKG and arrhythmias treated as needed; propranolol reportedly delays renal excretion of methylxanthines, so metoprolol is the beta-blocker of choice. Seizures may be controlled with diazepam or a barbiturate. In severe cases, clinical signs may persist up to 72 hours.

Xylitol

Xylitol is a sugar alcohol. It is used in sugar-free products such as gums and candies as well as for baking. It doesn't cause significant increases in blood glucose or insulin in humans. However, in dogs, xylitol causes a rapid, dose-dependant insulin release followed by potentially significant hypoglycemia. Signs can include vomiting, weakness, ataxia, depression, hypokalemia, seizures, and coma. Some dogs have developed liver dysfunction or failure following ingestion of xylitol although a link between xylitol and liver failure has not been established.

Treatment of xylitol ingestion by dogs should include emesis, provided that emesis can be performed very soon after ingestion—before clinical signs develop. A dog can show signs of hypoglycemia in as few as 30 minutes. Emesis performed after signs develop increase the risk of complications associated with vomiting such as aspiration. The efficacy of activated charcoal towards xylitol has is not known. Frequent small meals or oral sugar supplementation may be used to manage dogs not showing signs. If clinical signs of hypoglycemia develop, a bolus of IV dextrose followed by a dextrose CRI should be used to control moderate to severe hypoglycemia. Hypokalemia, likely secondary to insulin-induced movement of potassium into cells, should be treated if significant. Treatment should continue until blood glucose normalizes.