Managing the Mystery Poisoning Patient
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The practitioner is occasionally presented with a situation where it is suspected, either by the owner or the veterinarian, that an unidentified “poison” has intoxicated the patient. Although identification of the agent involved is often extremely helpful in determining proper treatment and prognosis, it is important to remember that the majority of these types of cases are managed without the offending agent ever being identified. Just because the identity of the toxicant remains a mystery does not mean that the veterinarian cannot deliver appropriate and effective treatment. Whether the toxic agent is known or not, it should always be remembered that the goal of the practitioner is to “treat the patient, not the poison.”

Assess the patient
Upon initial examination, evaluation of the animal for immediate life-threatening problems such as seizures, apnea/dyspnea, hemorrhage, cardiac arrhythmias, and hyperthermia is essential. A brief history may be obtained from the client while the examination is taking place—more detailed history may be obtained after the animal is stabilized. Additional important information that should be obtained includes duration of signs, age and prior health status of the animal, and any initial signs that are no longer apparent.

Stabilize the patient
Stabilization is a priority in animals presenting with severe clinical signs. Animals should be intubated and/or provided with supplemental oxygen as needed. If possible, obtain venous access and draw blood for laboratory profile and potential diagnostic testing (3 cc EDTA tube, 2 serum tubes are ideal), prior to administration of other medications. Standard anticonvulsants such as diazepam or barbiturates may be used to control seizures. Anticonvulsants, particularly benzodiazepines, should be administered slowly IV, as rapid administration may induce a dysphoric effect and temporarily exacerbate the situation. If the standard anticonvulsant therapy does not have any effect, consider inhalant anesthesia or a propofol CRI to allow for initial management of the patient.

Life-threatening cardiac arrhythmias should be treated as needed (atropine, propranolol, or lidocaine prn); arrhythmias not deemed immediately life-threatening can be treated after a better history has been obtained. Intravenous fluids and blood or blood replacement agents should be administered as needed. Body temperature should be normalized as needed, however aggressive cooling measures should be undertaken with care. Any electrolyte or acid/base abnormalities should be corrected. Once the patient has been fully stabilized, a more comprehensive physical examination may be performed.

Obtain history
Once the animal is stable, further questioning of the owner should be performed in an attempt to narrow down the possible causes for the animal’s signs. Questions to consider include how long since the last time the animal appeared normal to the owner, whether the onset of signs was gradual or sudden, the location of the animal in the last few hours prior to the development of clinical signs, and any history of administration of medications/herbal products/flea or tick control products to this animal or other animals in the household in the past 24 hours. The type of environment in which the animal lives (e.g. indoor only vs. indoor/outdoor vs. fenced yard vs. roaming) will help to determine the next lines of questions to ask.

For indoor animals, information that may be useful includes the areas to which the animal has access, the types of medications/herbal products (human and veterinary, prescription, illicit and OTC) available, whether there have been recent visitors who may have dropped medication, the types of houseplants in the home, whether there are children or teenagers in the household, presence of rodenticides or insecticides, and whether other pets in the house appear normal. In cases where illicit drugs are involved, or where owners have inappropriately administered medications or other products to their pets, the veterinarian may notice some reluctance on the part of the owner to provide the requested information. Tactful questioning may aid in obtaining the desired information. In other cases, it may be helpful to mention that without knowledge of the agent involved, more intensive (and expensive) diagnostics and treatments may be necessary.

For outdoor animals confined by fences or other means, identification of potentially toxic agents in outbuildings, garages or sheds to which the pet may have access is important. Other potential hazards found in yards include compost piles, plants, mushrooms, and yard treatments (especially some systemic insecticides and crabgrass killers). For free roaming animals, the challenge is much greater as the number of potentially toxic agents available is quite large. Determining whether the animal is in an urban, suburban, or rural environment and identifying the nature of the animal’s immediate surroundings (e.g. wooded areas vs. parks and lawns) may help in narrowing down the agents to which the roaming animal may have been exposed. The presence of livestock in the pet’s environment should stimulate questioning to determine the pet’s access to the barns or feed bins, whether medicated feeds, fly baits or feeds with...
growth promotants in them are present, whether the livestock have recently been medicated or dewormed, and if any livestock have recently been euthanized and buried on the property.

**Formulate rule-out list**

Armed with a thorough physical examination and as much history as is obtainable, the clinician should then formulate a list of differential diagnoses. It is important not to become so caught up in the certainty that the causative agent is a poison that one loses sight of potential etiologies of infectious, metabolic or other “non-toxic” origin. For instance, although a variety of toxicants may cause acute onset of seizures, other potential etiologies to consider include encephalitis, idiopathic epilepsy, hypoglycemia, head trauma, hypoxia, hepatic failure, acid/base abnormalities, etc.

**Ancillary support**

General supportive care includes maintaining hydration, ensuring adequate urine output, monitoring of respiratory, cardiac and neurologic status, and managing clinical signs as they develop. Recumbent or comatose animals require careful monitoring and thermoregulation. Gastrointestinal protectants or anti-emetics may be required (e.g. NSAID overdosages). Management of secondary hepatic or renal injury is imperative.

**Prevent toxicant absorption**

Decontamination should be instituted only after the animal has been fully stabilized. In clinically normal animals with suspected oral exposure to toxicants, emesis may be induced. Contraindications to emesis would include cases where animals have already vomited, are at risk of aspiration (e.g. CNS depression or other severe clinical signs), or have ingested corrosive agents, acids, alkalis, or hydrocarbons. In cases where animals are sedated or anesthetized (e.g. seizure control), gastric lavage may be considered; lavage is contraindicated if it is suspected that corrosive agents have been ingested. The gastric contents from spontaneous or induced emesis or gastric lavage should be kept in case analytical testing is desired in the future. Contents should be placed in a clean glass jar with a tight lid and kept refrigerated or frozen. If there could be possible legal action, seal with tape and initial/date sample. It is important to maintain records of chain of custody of samples (vomitus, carcass, etc.). Administration of activated charcoal is recommended for most cases of ingested poisons, although it is contraindicated in cases where oral exposure to potentially corrosive agents is suspected. For dermal exposures, animals should be bathed in liquid dish soap such as Dawn or Palmolive and rinsed copiously with warm water. Use of aprons, gloves and goggles by the veterinary staff during dermal decontamination will minimize human exposure to the toxicant.

"The antidote"

If, after stabilizing the animal and obtaining an adequate history, the toxic agent has been identified, specific antagonists may be indicated (e.g. Vitamin K for rodenticides). It is important to remember that the vast majority of toxic agents have no specific antidote, so the treatment will be, by necessity, symptomatic and supportive. Even in cases where antidotes do exist for the specific toxicant, there are often barriers to their use in veterinary medicine, including high cost and lack of availability (e.g. pamidronate for cholecalciferol or calcipotriene toxicosis).

**Analytic testing**

Unfortunately, there is no one test that will “screen” for all known toxicants, and multiple tests for specific agents can become costly. In general, one needs to have an idea of the general type of agent that may be involved before analytical testing is attempted. For suspected human medication ingestion, human hospitals may be willing to run tests for illicit drugs, antidepressants, cardiac drugs, acetaminophen, etc. on a STAT basis. Alternatively, there are now available in many human pharmacies, OTC home drug testing kits that might be considered; these bench-top tests, though technically not validated for non-humans, are quick, easy and cost-effective in cases of suspected exposure to certain human medications. For suspected rodenticide, insecticide, or heavy metal exposure, most veterinary diagnostic laboratories offer basic screens. Some diagnostic laboratories offer specialty screenings, such as “convulsant” screens that might detect agents such as bromethalin, tremorgenic mycotoxins, strychnine, etc. In many cases, the results from these tests may not be obtained for days, at which point the patient may be either recovered or dead. Therefore, the veterinarian should still be prepared to manage the case using appropriate symptomatic and supportive care.
Mood-Altering Drugs and Serotonin Syndrome
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With the large number of people and animals that are on antidepressant medications it is not surprising that the number of accidental ingestions of these drugs has also increased. Advances in medicine have lead to the development of medications capable of targeting specific biochemical mechanisms thought to be responsible for a variety of mental health disturbances. The increase in the number of drugs that affect serotonin metabolism reflects the discovery of the role of serotonin in maintenance of mental health. Serotonin has been determined to be involved with regulation of personality, sleep, temperature, sexual function, aggression, motor control, pain perception and cardiorespiratory function. Serotonin acts peripherally to stimulate smooth muscle and centrally as an inhibitor of excitatory neurotransmission. When overdosage of serotonergic drugs occurs, the result may be serotonin syndrome, a potentially life threatening multi-systemic disorder caused by over stimulation of serotonin receptors within the CNS and other systems.

Formation of serotonin
Serotonin is formed from tryptophan, an essential amino acid. Tryptophan, in competition with other amino acids, crosses the blood-brain barrier via a non-selective transporter mechanism. Within the CNS, tryptophan readily enters neurons and is subsequently converted to 5-hydroxytryptophan (HTP) by the enzyme tryptophan hydroxylase. This conversion is saturable and is the rate-limiting step in the formation of serotonin. The 5-hydroxytryptophan is then rapidly converted to serotonin (hydroxytryptamine). Serotonin is packaged in vesicles and released at the synapse during depolarization of the presynaptic neuron. Serotonin subsequently binds to receptors on the postsynaptic neuron, stimulating its depolarization or binds to receptors on the presynaptic neuron where it inhibits further release of serotonin. Its work accomplished, serotonin is pumped back into the presynaptic neuron, where it is either recycled into vesicles for future release or broken down to metabolites (primarily hydroxyindoleacetic acid) through the action of the enzyme monoamine oxidase.

Mechanism of action
With evidence that increasing brain serotonin levels may have antidepressant and anxiolytic effects in humans (and possibly other animals), many serotonergic drugs have been investigated. The drugs can be classified by how they effect serotonin (see Figure 1):

- Drugs that enhance serotonin synthesis (L-tryptophan, L-5-hydroxytryptophan)
- Drugs that increase presynaptic serotonin release (amphetamine, amphetamine derivatives, monoamine oxidase inhibitors [MAOIs], cocaine)
- Drugs that inhibit serotonin uptake into the presynaptic neuron (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], amphetamines, cocaine, dextromethorphan, meperidine)
- Drugs that inhibit serotonin metabolism (MAOIs)
- Drugs that act as serotonin agonists (buspirone, sumatriptin, LSD).

When these drugs do their jobs too well, or when overdoses occur, serotonin syndrome can result. The syndrome most commonly occurs in human when two or more serotonergic agents with different mechanisms of action are administered either concurrently or in close succession, leading to excessive levels of serotonin in the CNS. (see Table 1) Serotonin syndrome most commonly occurs in dogs secondary to inappropriate ingestion of the owner’s medications.

Clinical signs
Serotonin syndrome was originally classified in humans and defined as a constellation of symptoms that included at least three of the following: myoclonus, mental aberration (dementia, disorientation, etc.), agitation, hyperreflexia, tremors, diarrhea, ataxia and hyperthermia. This “classic” definition of serotonin syndrome has recently become controversial although a majority of cases of serotonin syndrome in humans and animals will fulfill these criteria.

In addition to the CNS and GI tract (where serotonin is a modulator of gastrointestinal smooth muscle contractility), respiratory and cardiovascular function may be altered in serotonin syndrome due to the importance of serotonin in maintaining vascular tone, stimulating bronchial smooth muscle, and stimulating cardiac stroke rate and volume. In general, these effects are not as clinically relevant as the GI and CNS signs. Alteration in platelet function or coagulation, both areas in which serotonin plays important role, has not been described in cases of serotonin syndrome in humans or animals.

In dogs the most common clinical signs include (in descending order): vomiting, diarrhea, seizures, hyperthermia, hyperesthesia, depression, mydriasis, vocalization, death, blindness, hypersalivation, dyspnea, ataxia/paresis, disorientation, hyperreflexia, and coma. Signs are similar, but vary in severity, whether 5-HTP or other serotonergic drugs such as SSRIs or MAOIs are ingested.
History of serotonin syndrome
The earliest account of serotonin syndrome in people was published in 1955, but the term serotonin syndrome was not used until 1982.

Diagnosis
There are no diagnostic tests to confirm serotonin syndrome, and the diagnosis will need to be based on history of ingestion of serotonergic drugs and presence of compatible clinical signs.

Decontamination
Emesis should only be attempted in asymptomatic animals. Gastric lavage may be used in cases of large ingestions. Most of the medications that can cause serotonin syndrome bind well to activated charcoal (lithium is the exception) and many times this is the only decontamination procedure needed. Repeated doses of activated charcoal may need to be used with ingestions of TCAs or other medications that undergo enterohepatic recirculation. A cathartic should be used along with the first dose of activated charcoal. Do not use magnesium salts as a cathartic in TCA ingestions as the decreased peristalsis caused by TCAs can result in increased magnesium absorption. An enema may also be given if sustained release products are consumed.

Treatment
Treatment of serotonin syndrome is largely symptomatic and supportive. Inducing vomiting is not recommended if clinical signs are present because of the increased risk of aspiration. Seizures and agitation generally respond to diazepam or phenothiazines (the drug of choice in humans), and barbiturates can be used in refractory cases. Because hyperthermia is a significant concern, cooling measures should be instituted. Diuresis does not enhance excretion, but intravenous fluids should be administered to support the cardiovascular system, aid in thermoregulation, and maintain renal blood flow. The use of cyproheptadine, a nonselective serotonin antagonist, has shown to be a helpful adjunct in managing serotonin syndrome in animals. Cyproheptadine may be administered at a dose of 1.1 mg/kg PO (dogs) or 2-4 mg PO (cats). In cases where the oral route is not feasible (e.g. severe vomiting), cyproheptadine may be crushed and mixed with saline to be instilled rectally. Doses of cyproheptadine may be repeated every 4-6 hours as needed until signs have resolved. Propranolol also has some serotonin blocking effect, and may be of benefit if animals are tachycardic. Administration of activated charcoal is important, but only once the animal has been reasonably stabilized. Metabolic acidosis may occur and can be corrected with sodium bicarbonate as indicated by blood gas analysis. Symptomatic care to control vomiting, abdominal pain, or other signs can be instituted as needed.

Prognosis
In most cases, signs will subside over 12 to 24 hours and full recovery is expected within 48 hours in uncomplicated cases. The outcome depends on dose, treatment, and exposure to other highly protein bound medications. The prognosis also depends on the overall health of the dog, especially if there is a history of liver and/or renal disease. Liver disease can inhibit metabolism of these drugs and renal disease can delay excretion. Potential sequelae include rhabdomyolysis, disseminated intravascular coagulation, and renal failure secondary to myoglobinuria. Prognosis is generally good with rapid and aggressive therapy.

Table 1. Serotonergic potential of various drugs

<table>
<thead>
<tr>
<th>High</th>
<th>Medium</th>
<th>Low</th>
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<tbody>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>Buspirone (BuSpar®)</td>
<td>Amantadine</td>
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<tr>
<td>Clomipramine (Clomicalm®, Anafranil®)</td>
<td>Cocaine</td>
<td>Bromocriptine (Parlodel®)</td>
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<tr>
<td>Dexfenfluramine (Redux®)</td>
<td>Desipramine (Norpramin®)</td>
<td>Bupropion (Wellbutrin®, Zyban®)</td>
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<td>Dextromethorphan</td>
<td>Doxepin (Adapin®, Sinequan®)</td>
<td>Carbamazepine (Tegretol®)</td>
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<td>Fenfluramine (Ponderal®)</td>
<td>L-Dopa</td>
<td>Codeine</td>
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<td>Fluoxetine (Prozac®)</td>
<td>LSD (lysergic acid diethylamide)</td>
<td>Melatonin</td>
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<td>Fluvoxamine (Luvox®)</td>
<td>Nortriptyline (Pamelor®)</td>
<td>Mirtazapine (Remeron®)</td>
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<td>Imipramine</td>
<td>Trazodone (Desyrel®)</td>
<td>Nefazodone (Serzone®)</td>
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<tr>
<td>Isocarboxazid (Marplan®)</td>
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<td>Pentazocine (Talwin®)</td>
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<tr>
<td>Lithium</td>
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<td>Pergolide (Permax®)</td>
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<tr>
<td>MDMA (methyleneoxyamphetamine)</td>
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<td>Tramadol (Ultram®)</td>
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<td>Meperidine</td>
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<td>Moclobemide (Manerix®)</td>
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<td>Paroxetine (Paxil®)</td>
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<td>Phenelzine (Nardil®)</td>
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<td>Selegiline (Anipryl®, Eldepryl®)</td>
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<td>Sertraline (Zoloft®)</td>
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<td>Tranilcipromine (Parnate®)</td>
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<td>Venlafaxine (Effexor®)</td>
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The good

Silica gel packs
Desiccant packs are included as moisture absorbents. Most ingestions will not cause clinical signs, although a mild gastrointestinal upset may occur.

Ant and roach baits
Ant and roach baits are common objects found in households. The insecticides used most commonly in these baits are fipronil, avermectin, sulfuramid, boric acid, indoxacarb and hydramethylfuron, all of which are of low mammalian toxicity and present in very low concentrations within the baits. The baits also contain inert ingredients such as peanut butter, breadcrumbs, fats and sugar to attract the insects; these agents are also sometimes attractive to pets.

Birth control pills
Birth control pills generally contain estrogen and progestins. Estrogen doses of less than 1 mg/kg are not of concern. At higher doses, bone marrow suppression may be seen.

Glow-in-the-dark sticks and jewelry
The primary luminescent agent in these types of products is dibutyl phthalate (n-butyl phthalate), an oily liquid that is also used as a plasticizer and insect repellent. Dibutyl phthalate is of low toxicity (LD$_{50}$ >8000 mg/kg in rats) but has an extremely unpleasant taste. Taste reactions are commonly seen.

Toilet water (tank drop-ins)
Tank "drop in" products typically contain anionic/nonionic detergents, cationic detergents, bleach, and/or acids. However, when a tank "drop in" cleaning product is used in a toilet, dilution occurs and the cleaning agent is just a gastric irritant.

Cyanocrylate glues
Cyaanoacrylates (Super Glue®) solidify when they contact saliva, so minimal absorption occurs.

Fertilizers
Fertilizers are made up of nitrogen, phosphorus, and potassium (NPK) in various ratios. Fertilizers generally have a wide margin of safety and only mild GI signs are expected after ingestion. Additives to fertilizers may include herbicides, insecticides, fungicides, iron, copper, and zinc. These additions increase the likelihood of GI and systemic signs.

The bad

Anticoagulants
Anticoagulants in use as rodenticides today are almost all second-generation derivatives. They inhibit the activity of vitamin K epoxide reductase, which converts vitamin K epoxide to the active reduced form. This reduced vitamin K is crucial to activation of clotting factors II, VII, IX, and X.

Any exposure > 0.02 mg/kg of a second generation anticoagulant requires treatment and evaluation. Emesis can be induced if ingestion has occurred within the last 4 hours. If little or no bait is recovered, administration of activated charcoal is next. Another option is to institute Vitamin K1 therapy (2.5-5 mg/kg/day) or monitor PT tests. 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.

Early signs of anticoagulant toxicity are vague, and depend on the site of a bleed. Lethargy, non-productive cough, intermittent lameness, mild anemia, or even sudden collapse can be seen. Petechiae and ecchymoses 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.

If the animal is actively bleeding, start vitamin K1 and give clotting factors via a whole blood transfusion, fresh frozen plasma, or fresh plasma. Minimize physical activity throughout therapy.

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.

Bromethalin is rapidly absorbed from GI tract. Cats are far more sensitive to this agent than are dogs. 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.

**Cholecalciferol**

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.

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. Multiple doses of activated charcoal and cholestyramine can help decrease absorption.

Treatment is aimed at lowering the serum calcium and phosphorus levels, 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 calcitria. Monitor serum calcium, phosphorus, BUN and creatinine daily to judge effectiveness of therapy. If calcium levels are rising despite calciiuresis, 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. 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).

**Zinc phosphide**

Zinc phosphide is an old rodenticide posing as a new one. 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 damage is in tissues with the highest oxygen demand – brain, lungs, liver and kidney.

Lethal doses for 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 than 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 toxicosis.

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 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 includes IV fluids to maintain blood pressure renal perfusion, and gastroprotectants. 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 described 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.

**Corrosives: Acids, alkalis, cationic detergents**

Products containing acids, alkali or cationic detergents can cause local corrosive damage. Clinical signs occur almost immediately upon exposure with acids, but can be delayed up to 12 hours with alkalis or cationics. Oral exposure results in pain, vocalization, dysphagia, vomiting (+/- blood), and irritation or ulceration of oral and/or esophageal mucosa. Significant hyperthermia (>104° F) may accompany oral inflammation.
Batteries
When batteries are chewed and the alkaline gel is released, liquifactive necrosis results (see Alkali section). Foreign body obstruction may occur when casings are swallowed and disc batteries may be inhaled, resulting in acute dyspnea and cyanosis.

Pennies
Ingestion of pennies can result is zinc toxicosis. In the stomach, gastric acids leach the zinc from its source, and the ionized zinc is readily absorbed into the circulation, where it causes intravascular hemolysis.

Polyurethane adhesives
Isocyanate glues (Gorilla Glue®, Elmer’s ProBond Polyurethane Adhesive®) are expanding wood glues that have been associated with gastric foreign bodies.

The tasty

Bread dough (yeast)
Rising yeast bread dough produces carbon dioxide and ethanol. This can result in bloated drunk dogs.

Chocolate
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 (see Table 1).

Macadamia nuts
Macadamia nut ingestion in dogs can cause weakness, depression, vomiting, ataxia, tremors, transient paresis, and hyperthermia. Most animals return to normal within 48 hours.

Avocados
Species sensitivity among animals varies. In dogs and cats, avocados are likely of low toxicity. In other species, sterile mastitis and myocardial necrosis can occur.

Moldy food (tremorgenic mycotoxins)
Tremorgenic mycotoxins produced by molds on foods are a relatively common, and possibly under-diagnosed, cause of tremors and seizures in pet animals. These molds grow on practically any food, including dairy products, grains, nuts, and legumes; compost piles may also provide a source of tremorgens. Clinical signs include fine muscle tremors that may rapidly progress to more severe tremors and seizures.

Table 1. Methylxanthine levels of various chocolates

<table>
<thead>
<tr>
<th>Compound</th>
<th>Theobromine</th>
<th>Caffeine</th>
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</thead>
<tbody>
<tr>
<td>White Chocolate</td>
<td>0.25</td>
<td>0.85</td>
</tr>
<tr>
<td>Milk Chocolate</td>
<td>58</td>
<td>6</td>
</tr>
<tr>
<td>Semi-sweet Chocolate chips</td>
<td>138</td>
<td>22</td>
</tr>
<tr>
<td>Baker’s Chocolate (unsweetened)</td>
<td>393</td>
<td>47</td>
</tr>
<tr>
<td>Dry cocoa powder</td>
<td>737</td>
<td>70</td>
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New Antidotal Therapies
Tina Wismer, DVM, DABT, DABVT
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Antidotes can be divided into three broad categories: chemical antidotes, pharmacologic antidotes, and functional antidotes. Chemical antidotes act directly on the toxicant to make it less toxic and/or more readily excreted. Pharmacologic antidotes antagonize toxic agents at their receptor sites or through other macromolecules. Functional antidotes are agents that act on the symptoms of poisoning. In many cases, these antidotes have no real effect on the toxicant itself, but they lessen the severity of the clinical picture of the intoxicated patient.

Chemical antidotes: chelators
Deferoxamine (Desferal®, Ciba) is a chelating agent approved for use in humans for the treatment of acute iron poisoning, chronic iron overload and treatment of chronic aluminum overload in patients on chronic dialysis. It has been used off-label to treat iron toxicosis in animals. Deferoxamine forms a chelate complex with free iron, which is then excreted in the urine and bile. Deferoxamine is most effective within the first 24 hours, before the iron has been distributed to the tissues. The extrapolated animal dose for iron toxicosis is 40 mg/kg, IM, every 4-8 hours. The IM route is preferred, as too rapid IV administration can cause hypotension and pulmonary edema. The efficacy of deferoxamine can be increased by giving ascorbic acid after the gut has been cleared of iron. The deferoxamine-iron complex gives a salmon pink color to the urine (“vin rose”). Continue to chelate until urine clears or until serum iron levels return to normal.

DMSA (2,3-dimercaptosucinic acid, succimer)
Succimer (Chemet®, McNeil Consumer Products) is approved for the treatment of childhood lead poisoning. It has also been used to treat arsenic and mercury poisoning and does not bind iron, calcium or magnesium. Succimer is available as 100 milligram capsules. It is a structural analog to BAL (British Anti-Lewisite, dimercaprol) but has less potential to cause nephrotoxicity. Succimer is preferred over Ca-EDTA and penicillamine, as succimer can be given while lead is still in the GI tract (the other 2 increase lead absorption), it comes in an oral form, it has a lower incidence of causing GI upset and it is also less likely than the others to induce Zn deficiency. Succimer, however, is more expensive than the other options (capsules are approximately $4 apiece).

Although not approved for animal use, there are published doses for treating lead toxicosis. The dose for dogs and cats is 10 mg/kg PO TID for 10 days (administer on empty stomach; per rectum if animal is vomiting). Dosing for caged birds is 25-35 mg/kg PO BID 5 days a week for 3-5 weeks. Higher doses (80 mg/kg) have caused death in cockatiels. It is not uncommon for there to be a post-chelation rebound (or elevation) of blood lead levels. Most of the time, this is due to redistribution of the lead from bone and tissue stores in animals chronically exposed to lead. If lead levels are still increased and the animal is still symptomatic, a repeated round of therapy can be pursued. If the animal is asymptomatic, there is no need to retreat.

Chemical antidotes: immunotoxicotherapy
Crotalidae polyvalent immune FAB (Ovine)
Crotalidae polyvalent immune Fab (ovine) (CroFab®, Fougera) is approved for the management of patients with North American crotalid snake envenomation. The antivenin has been shown to cross react with 10 North American crotalid species (see Table 1). In a recent study, CroFab® was given to 115 dogs presented to several veterinary emergency hospitals in the western US. The CroFab® gave “excellent results” although some dogs did require more than one vial (average dosing was 1.25 vials). This study also reported significantly less reactions to the CroFab® product compared to Ft. Dodge/Wyeth equine antibody antivenin (advantage of Fab over whole IgG).

Early use (within 6 hours of snakebite) is recommended to prevent clinical deterioration and the occurrence of systemic coagulation abnormalities. CroFab Dil is diluted in 250 mL of saline and infused over 60 minutes, with monitoring for development of an allergic reaction during the first 10 minutes. Recurrence of local symptoms of crotaline envenomation following CroFab® treatment has been reported in people, probably due to the short half-life of the antivenin. Cost is approximately $1400/2 vials.

Digoxin immune Fab
Digoxin immune Fab (Digibind®, Burroughs Wellcome) is produced from specific digoxin antibodies from sheep and will bind directly to digoxin or digitoxin and inactivate it. Antidigitoxin Fab fragments have an affinity for digoxin that is much higher than the affinity of digoxin for its sodium-potassium ATPase target. Digibind® has sufficient cross reactivity and can also be effective against bufotoxins (Bufo toads) and plants containing cardiac glycosides (see Table 2).

Treatment with Fab fragments should be considered in those patients who fail to respond to conventional therapy. Signs of severe toxicity might include severe ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation), progressive bradyarrhythmias
(severe sinus bradycardia), or second or third degree heart block not responsive to atropine. The dosage varies based on the amount of digoxin to be neutralized. The best situation is to have a human hospital run digoxin levels and then dosing is based on those results. The dose of Digibind® is calculated: Digibind® dose (number vials) = [Serum Digoxin Concentration (ng/mL) x Patient’s weight (kg)] / 100. The next best method is to estimate the body load of digoxin ingested (almost impossible with toads or plants). Body load is estimated as dose ingested x 0.8. The formula is then: Digibind® dose (number vials) = [Body load (mg) / 0.5 (mg/vial)]. If either of these methods are not feasible then it is suggested that 1-2 vials be administered and the effects observed. Each vial of Digibind® contains 38 mg which will bind approximately 0.6 mg of digoxin or digitoxin. Reconstitute each vial with 4 mL of sterile water or isotonic saline. Administer slow IV over 30 minutes, infused through a 0.22 micron filter (if possible). Digibind® can be a life saving treatment however, it is expensive ($2200/5 vials).

Chemical antidotes: enzyme inhibitors

**Fomepizole (4-MP, 4-methylpyrazole)**

Fomepizole (Antizol-Vet®) is a competitive inhibitor of alcohol dehydrogenase. It was approved for use in dogs to treat ethylene glycol (EG) toxicosis in 1997. Each vial contains 1.5 g of fomepizole and the reconstituted solution is 50 mg/ml. Shelf life is 72 hours once reconstituted. The advantages of fomepizole are that it does not induce hyperosmolality, CNS depression, and diuresis (vs. ethanol). Dogs may be treated as late as 8 hrs post ingestion and still have a favorable prognosis. Fomepizole may still be effective as late as 36 hrs post-ingestion of EG. The recommended dosing regime for dogs is an initial IV injection of 20 mg/kg (give over 15-30 minutes), followed by 15 mg/kg slow IV at 12 hours and again at 24 hours. A last dose of 5 mg/kg IV is given at 36 hours after the first injection. Since fomepizole slows down the metabolization of EG, serum levels may still be detectable at 72 hours after ingestion. If the EG test is still positive after the last dose continue treatment at 5 mg/kg IV every 12 hours until test is negative.

Fomepizole is not labeled for cats but preliminary clinical trial results suggest that high doses of fomepizole in the cat (125mg/kg slow IV infusion loading, then 31.25 mg/kg at 12, 24, 36 hrs post EG ingestion) are safe and effective when therapy is initiated within 3 hours following EG ingestion. [Note: at 3 hrs post lethal dose EG administration, 100% recovery with fomepizole, 25% recovery with ethanol. At 4 hrs post EG, 100% mortality with fomepizole and ethanol was noted in these studies]. Other than calcium oxalate crystals in the urine, no biochemical evidence of renal impairment was noted out to 2 weeks post EG exposure and fomepizole.

Pharmacologic antidotes: receptor antagonists

**Flumazenil**

Flumazenil (Romazicon®, Roche) is an imidazobenzodiazepine derivative, which antagonizes the CNS actions of benzodiazepines. Flumazenil binds to and rapidly displaces benzodiazepines from the benzodiazepine receptor, thereby reversing their sedative and anxiolytic effects within 1-2 minutes. It is indicated in people for diagnosis of benzodiazepine overdose and reversal of benzodiazepine sedation and respiratory depression. Use in animals is usually limited to those at risk of respiratory depression. The dose is 0.01 mg/kg, IV, for both dogs and cats and can be repeated if severe depression returns. The half-life for flumazenil is about 1 hour, so repeated injections may be needed. Flumazenil may also be given intratracheally in an emergency situation. Flumazenil is contraindicated in patients suspected of tricyclic antidepressant overdoses as it can cause seizures.

**Atipamezole**

Atipamezole (Antisedan®, Pfizer) is an α2-adrenergic antagonist labeled for use as a reversal agent for medetomidine, but it can also be used to treat several toxicoses. Atipamezole can be used to reverse other α2-adrenergic agonists (amitraz, xylazine, bromonidine, clonidine and tizanidine). Atipamezole quickly reverses the hypotension and bradycardia seen in these toxicoses. After IM administration in the dog, peak plasma levels occur in about 10 minutes. Atipamezole has an average plasma elimination half life of about 2-3 hours (vs. yohimbine half life of 1.5-2 hr in dogs) and may need to be repeated.

Functional antidotes

**Bisphosphonates**

Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. Pamidronate (Aredia®, Novartis) inhibits osteoclastic bone resorption and was developed to treat hypercalcemia of malignancy in people. Pamidronate can be used in dogs for treating hypercalcemia secondary to cholecalciferol toxicosis. The recommended dose of pamidronate for dogs is 1.3 - 2.0 mg/kg as a slow IV infusion in 0.9% sodium chloride over 2-4 hours. The advantage of pamidronate over salmon calcitonin is that it has long lasting effects (may need to repeat once in 5-7 days). Do not use in combination with calcitonin. The downside of pamidronate is that it is expensive ($275-400/vial), however, when compared to length of hospitalization and the labor involved in the repeated doses of calcitonin, the cost is comparable.
New antidotal uses for other drugs (teaching old dogs new tricks)

Intralipids
Intralipids are lipid emulsions. Lipid emulsions are commonly used as a fat component for parenteral nutrition. While more studies are needed, lipid therapy is very exciting new treatment for lipid soluble toxicoses. Lipid use is based on human research investigating bupivacaine overdoses. The possible mechanism for lipid rescue is that the lipids bind to the fat soluble toxin ("lipid sink") and bound toxin is inactive.

Liposyn, or any other 20% lipid solution, can be given through a peripheral catheter and is relatively inexpensive. A bolus of 1.5 ml/kg is given (over 1 minute if cardiac arrest, slower otherwise), followed by 0.25 ml/kg/min for 30-60 minutes. This is repeated in four hours if the serum is clear. Lipid therapy can hasten recovery time in some cases.

There are possible complications to lipid therapy: significant lipemia, pancreatitis, transiently increased liver enzymes, volume overload and lipids can also remove antidotes and other therapies.

Cholestyramine
Cholestyramine is an anion exchange resin available by prescription only. It is used to lower cholesterol in patients who have not responded to normal therapies. Cholestyramine has been used in human medicine to aid in the treatment of toxicoses (amiodarone, digitoxin, chloroquine, methotrexate, piroxicam, vitamin D, warfarin, blue-green algae, indomethacin). It binds with bile acids in the intestine, preventing their reabsorption. This stops enterohepatic recirculation. Cholestyramine is not absorbed out of the digestive tract, so it has no systemic effects, but constipation and mild liver enzyme elevation may be seen. The dose is 0.3 – 1 g/kg TID for several days (depends on toxin ingested). For our patients, the powder should be given or mixed with canned food. Cholestyramine is cost effective with a price around $50-80 for 240g.

Cyproheptadine
Cyproheptadine (Periactin®, Merck) is an antihistamine (H1 blocker) that also has serotonin antagonistic activity. Cyproheptadine has been used in veterinary medicine for its antihistaminic and appetite-stimulant effects (cats) and is now being used to help treat serotonin syndrome. Serotonin syndrome is a condition caused by serotonin excess within the CNS and is characterized in dogs by tremors, seizures, hyperthermia, ataxia, vomiting, diarrhea, abdominal pain, excitement or depression, and hyperesthesia. Serotonin syndrome has been associated with the use of drugs that increase brain serotonin levels (e.g. selective serotonin reuptake inhibitors, amphetamines) in humans and after accidental ingestion of 5-hydroxytryptophan (serotonin precursor) in dogs. The recommended dose for dogs is 1.1 mg/kg PO or per rectum every 1-4 hours until signs subside.

N-acetylcysteine
N-acetylcysteine (NAC, mucomyst) is the N-acetyl derivative of L-cysteine, a naturally occurring amino acid. Although originally used as a mucolytic agent in people, NAC has become an important part of managing acetaminophen overdoses in people and animals. Because of NAC’s ability to minimize oxidative damage to the liver from acetaminophen, NAC had been investigated for its ability to prevent damage from other hepatotoxins. A recent study on Amanita phalloides (death cap mushroom) poisoned people showed that the use of a protocol similar to that used for acetaminophen toxicity (high dose) was effective in preventing permanent hepatic injury in 10 of 11 people.

Dantrolene
Dantrolene (Dantrium®, Procter & Gamble Pharm.) has been mostly used in veterinary medicine for the prevention and treatment of malignant hyperthermia syndrome. Dantrolene may also be used to treat the malignant hyperthermia-like reaction seen in dogs after the ingestion of hops (Humulus lupulus). Hops are used in the brewing of beer. Recommended dose of dantrolene is 2-3 mg/kg, IV, or 3.5 mg/kg, PO, as soon as possible after ingestion.

<table>
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<tr>
<td>Urginea maritima</td>
<td>Squill</td>
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Herbal preparations are increasing dramatically in usage. A recent survey (2007) discovered that 38% of adults and 12% of children in the US have used at least one alternative therapy over the preceding 12 months. Many people not only use alternative therapies themselves, but also give various therapies to their pets, with or without advice from a veterinarian. The odds are that at least some clients in an average practice will have an interest in, or ask about the use of alternative medicine. The regulation of herbs and other dietary supplements differs from most pharmaceutical drugs. In 1994, the Dietary Supplement and Health Education Act (DSHEA) was created. This act includes vitamins, minerals, and herbs. Under the DSHEA, supplement manufacturers are not required to prove efficacy, safety, and there are no mandated quality controls. The FDA can intervene if enough adverse reactions to a specific product occur, but the burden of proof is on the FDA to prove a particular product is harmful. Manufacturers are allowed to state what effect a product is expected to produce (such as the antidepressant effects produced by St. John’s Wort) but the manufacturer cannot claim a product specifically cures a stated effect. The label must include the statement that the claims have not been evaluated by the FDA.

Ma Huang, Sida cordifolia, and Citrus aurantium
Ma Huang is produced from Ephedra sinica, as well as other Ephedra species and herbs such as Sida cordifolia. Other common names of ma huang include yellow horse and sea grape. S. cordifolia is often known as Indian common mallow. Bitter orange, Citrus aurantium, contains synephrine. Historically, ma huang has been used to treat asthma, colds and flu, fevers, congestion and coughs. Today, ma huang is frequently used as a weight-loss aid because of its stimulant properties and as a decongestant because it is vasoconstrictive. Ma Huang is also abused, like an illicit drug, because of its hallucinogenic and stimulant properties. When used as a weight-loss aid, frequently caffeine-containing plants are included in the formulation, which can increase toxicity. Some formulations will list the quantity of ephedrine per unit of drug. The active components of Ephedra sinica and Sida cordifolia are alkaloids, including ephedrine and pseudoephedrine. The FDA has banned Ephedra containing substances, but did not specifically list the active constituents. Products containing S. cordifolia and bitter orange cause the same clinical syndrome as those containing Ephedra.

Pharmacologically, ephedrine is a sympathomimetic alkaloid. The alkaloids stimulate alpha- and beta-adrenergic receptors, causing the release of endogenous catecholamines at synapses in the brain and heart. This stimulation results in peripheral vasoconstriction and cardiac stimulation. This results in increased blood pressure, tachycardia, ataxia, restlessness, tremors, and seizures.

Guarana
Guarana is the common name of Paullinia cupana, a plant containing high levels of caffeine. Guarana may contain 3% to 5% caffeine by dry weight compared to coffee beans (1-2 % caffeine) and tea (1-4 % caffeine). Common names include Brazilian cocoa and Zoom. Theobromine and theophylline have also been found in the plant. Historically, guarana was used to provide energy during fasting, as an aphrodisiac, and to prevent malaria and dysentery. Guarana is frequently found in herbal weight loss aids (with or without ma huang) and in products promising increased energy. Because guarana contains methylxanthines, it produces a clinical syndrome similar to chocolate, coffee, or over the counter stimulant products which contain caffeine.

Caffeine is a methylated xanthine. It increases cyclic AMP, releases catecholamines, and increases muscular contractility. The net effect is a positive inotropic and chronotropic effect on the heart, cerebral vasoconstriction, renal vasorelaxation, and smooth muscle relaxation in the gastrointestinal tract. Clinical signs include vomiting, restlessness and hyperactivity, polydipsia and polyuria. Tachycardia and other cardiac arrhythmias such as premature ventricular contractions (PVCs), are possible. Clinical signs progress to muscle tremors and seizures, and finally death.

Griffonia simplicifolia
Griffonia simplicifolia seeds are used as a source of 5-hydroxytryptophan (5-HTP). This extract is generally used to treat depression, headaches, obesity and insomnia in humans. 5-HTP is reported to increase serotonin in the CNS. Label information may list 5-HTP, 5-hydroxytryptophan, or griffonia seed extract as an ingredient. Drug interactions with MAO inhibitors, antidepressants, and herbs such as St. John’s Wort can occur. 5-HTP is rapidly and well absorbed from the gastrointestinal tract. 5-HTP readily crossed the blood-brain barrier. Once target cells are reached, 5-HTP is converted to serotonin (5-hydroxytryptamine). Serotonin is important in the regulation of sleep, cognition, behavior, temperature regulation, and other functions. Clinical signs resemble serotonin syndrome in humans. Signs include seizures and tremors, depression, ataxia, and hyperesthesia. Gastrointestinal effects including vomiting, diarrhea, and drooling are common. Severe hyperthermia and blindness have been reported.
**Yohimbine**
Yohimbine is derived from the bark of *Pausinystalia yohimbe*. It has long been considered an aphrodisiac, and the bark was smoked as a hallucinogen. In traditional medicine, angina and hypertension were treated with yohimbine. Today, it is mostly used as a sexual stimulant, and is frequently marketed as herbal Viagra. Pharmacologically, yohimbine is classed as an alpha 2-adrenergic blocking agent. A first pass effect can be seen, and the drug is metabolized in the liver. Metabolites are eliminated in the urine. The T1/2 in dogs is 1.5-2 hours. In large doses, severe and life threatening clinical signs can be seen. Clinical effects are related to the alpha 2 blockade and subsequent CNS and cardiovascular stimulation. Clinical signs include hyperactivity, agitation, tremors, seizures, vomiting, diarrhea, abdominal pain, hypertension initially followed by a profound hypotension.

**Alpha lipoic acid**
Alpha lipoic acid is a fat-soluble, sulfur-containing antioxidant. A variety of synonyms exist including lipoic acid, thioctic acid, acetate replacing factor, biletan, lipoicin, thiocitaid and thiodcan. Alpha lipoic acid is found in a variety of foods, especially yeast and liver. Spinach, broccoli, potatoes, skeletal muscle and organ meats like the heart and kidney are also good sources. In toxicology, alpha lipoic acid is useful in treating amanita mushroom poisoning. In veterinary medicine, it is used to treat diabetic polyneuropathy, cataracts, glaucoma, and ischemia-reperfusion injury. Alpha lipoic acid is synergistic with insulin, causing decreased blood sugar and increasing liver glycogenesis, and facilitates glucose uptake into cells. Clinical signs of toxicity include vomiting, ataxia, cataracts, glaucoma, and ischemia-reperfusion injury. Alpha lipoic acid is found in a variety of foods, especially yeast and liver.

**Chamomile**
Chamomile refers to both German chamomile (*Matricaria recutita*) and Roman chamomile (*Chamaemelum nobile*). Common names for German chamomile include wild chamomile and pin heads. Common names for Roman chamomile include garden chamomile, sweet chamomile, ground apple and whig plant. The plant is indigenous to Europe and northwest Asia and naturalized in America. German chamomile is an annual and Roman chamomile is a slow growing perennial. The plant is erect and grows to about 20-40 cm. Flowers are white with yellow centers. Chamomile has been used since the Roman empire. It was used as an anti-spasmodic and sedative. In folk medicine, chamomile is used for rheumatism and intestinal parasitism. Chamomile has also been used as a hair tint and cigarette flavoring. In veterinary medicine, the most common uses are as a natural wormer, sedative, and as a treatment for aggression.

Chamomile contains essential oils, flavanoids, and hydroxycoumarins. Bisabolol, which accounts for 50% of the essential oils found in chamomile, has an acute LD₅₀ of 15 ml/kg in rats and mice. Chronic ingestion in cats can cause epistaxis and hematomas due to the hydroxycoumarin content.

**St. John’s Wort**
St. John’s wort (*Hypericum perforatum*) is also known as goatweed, rosin rose, and Klamath weed. Traditionally, this herb is used as an antidepressant, to treat diarrhea and gastritis. It was also used to treat insomnia and cancer. In veterinary medicine, this plant is well known for causing photosensitization in livestock and horses. St. John’s wort has been responsible for devastating economic losses. The major active constituents are anthraquinone derivatives, hypericin and pseudohypericin, as well as flavanoids.

**Valerian root**
Valerian root (*Valeriana officianalis*) is one of the most popular herbs on the market. Common names include all-heal, heliotrope, Vandal root, and Capon’s tale. It is an herbaceous perennial found widely over the United States. The primary active ingredients are volatile oils, alkaloids, and most importantly, valepotriates. The root is the only part of the plant that is used. Valerian is classed as generally recognized as safe (GRAS) for food use. The volatile oils are used as flavoring in some food products. Valerian is used primarily as a sedative, and as a sleeping aid. It has also been used in epilepsy, headaches, colic, and numerous other minor ailments. Valerian is frequently taken as a tea, or as an extract. Valerian increases the length of sedation induced by pentobarbital and length of anesthesia produced by thiopental. Valerian has helped ease the effects of withdrawal from benzodiazepines due to similar receptor sites but increases the effects of sedatives if taken concomitantly. Most reports of adverse effects of valerian in human literature occur after chronic use. These effects include headache, cardiac arhythmias, and agitation. In one case report, 200 mg in a human caused fatigue, tremors, abdominal pain, and mydriasis. Animal studies included injections of 50 mg/kg intravenous in cats which caused a drop in heart rate and blood pressure. Another study found no pharmacological effect in cats at 250 mg/kg. Mice given up to 4600 mg/kg orally produced mild clinical effects. Signs of toxicity included ataxia, hypothermia, and muscle relaxation. The ASPCA Animal Poison Control Center has had only a few calls on valerian ingestion. Most produced no clinical effects, although lethargy and sedation was seen in a cat.
Garlic

Garlic (Allium sativum) is most often used in cooking. Other common names include stinking rose, treacle, nectar of the gods, and camphor of the poor. The fresh bulb, dried bulb, and liquid extract of the bulb are all used. Historically, garlic has been used to treat diseases ranging from leprosy to clotting disorders in horses. Garlic powder used to be a standard tuberculosis treatment. The volatile oils in garlic contain the active ingredients, a sulfur containing compound and allicin. The majority of pharmaceutical activity is believed to be found in these substances. Garlic has been used to treat high cholesterol, hypertension, as well as the common cold and diabetes. Garlic is contraindicated if gastrointestinal ulcers or inflammation is present. Patients with hypothyroidism should also avoid garlic. It is theorized that consumption of high levels of purified active constituents may cause reduced iodine uptake by the thyroid. Due to increased clotting times, garlic should be avoided prior to surgery. Since garlic can have a hypoglycemic effect, insulin dosages should be monitored carefully. Anticoagulant effects of warfarin may be enhanced by garlic use and clotting times require additional monitoring. Garlic is in the same family as onions and a similar toxic effect would be expected. Onion toxicity results in weakness, tachypnea and tachycardia. Hematological changes including hemolysis, Heinz bodies, and possibly methemoglobinemia may occur.

Essential oils

Essential oils are produced by a large number of plants. The oils are a mixture of terpenes and other chemicals. Essential oils are used from food flavorings to perfumes to medications. The most commonly used essential oils in veterinary medicine include Melaleuca or tea tree oil (Melaleuca alternifolia), pennyroyal oil (Mentha pulegium), D-limonene and linalool (Citrus spp.), Citronella (Cymbopogum nardus), Thuja (Thuja occidentalis), and wormwood or absinthe (Artemisia absinthium). In veterinary medicine, essential oils are most commonly used to treat flea infestations, hot spots or other dermatological conditions, or as wormers. Oils may be found in shampoos, dips, liniments, teas, tinctures, syrups, or other formulations. Cats appear to be more sensitive to essential oils than dogs. The most common clinical signs after dermal exposures include ataxia, muscle weakness, depression, and behavioral abnormalities. Severe hypothermia and collapse have occurred in cats. A transient paresis can occur in small breed dogs when melaleuca oil is applied down the spine as a topical flea treatment. Cats have developed scrotal dermatitis after exposure to D-limonene or linalool. Liver failure is associated with essential oils, especially pennyroyal and melaleuca. Oral ingestions cause vomiting and diarrhea. Central nervous system depression may occur, and seizures are possible with large doses. Aspiration pneumonia can occur when essential oils are inhaled. Death can occur with sufficient doses. Signs usually develop from almost immediately up to eight hours post exposure.

Grapefruit seed extract

Grapefruit seed extract (GSE) is being touted as a disinfectant, to cure fungal disease, external parasites, and many other conditions. GSE is made from the pulp and seeds of grapefruit. The final product is acidic, and contains quaternary compounds similar to cationic detergents. Severity of injury typically depends on the concentration of the product and the duration of the contact. Primary clinical signs include hypersalivation, vomiting with possible hematemesis, muscular weakness. Fasciculations and CNS depression may occur. Diarrhea, dermal necrosis or dermatitis, pulmonary edema, and hypotension are possible. Corrosive burns can occur in the mouth, especially on the tip and sides of the tongue, pharynx and the esophagus. Hyperthermia is common in cats.

Summary

When a decision has been made to use an alternative therapy, quality assurance is critical. Herbal medications should be treated as medications, with appropriate precautions. Veterinarians should encourage clients to discuss alternative therapies with them. Choice of therapies, diagnoses, and clients expectations should be discussed. Encourage clients to learn the facts behind CAM (complementary and alternative medicine) therapies. When discussing information obtained from web sites, suggest clients use the C.R.E.D.I.B.L.E. evaluation criteria developed by Dr. Gunther Eysenbach.: Current and frequent updates References cited Explicit purpose and intentions of the site Disclosure of sponsors Interests declared and not influencing objectivity (eg financial interests) Balanced content, listing advantages and disadvantages Labeled with metadata Evidence level indicated.
Managing Toxicosis in Exotic Species
Tina Wismer, DVM, DABT, DABVT
ASPCA Animal Poison Control Center
Urbana, IL

Our exotic animal pets can present a challenge with some of their differences in physiology. However, the same adage remains…treat the patient, not the poison. Take a complete history while the patient is being stabilized in the incubator with oxygen. The history should include information such as whether the animal has been exposed to infectious disease or toxins; the animal’s environment, diet, reproductive status, and previous illness; husbandry practices should be discussed. Environmental history includes information about caging, flight capabilities (in birds), and exposure to toxins.

Most decontamination techniques transfer easily from one species to another. Stress is a big killer of our exotic animal patients. Taking it slow and allowing down time can help reduce stress. Sedatives and anesthesia can make managing decontamination much easier for you and the animal.

**Emesis**
Do not induce vomiting in species that cannot vomit (rabbits, rodents, marsupials, birds, ruminants). It is OK to induce vomiting in pot bellied pigs and ferrets.

**Adsorbents**
When administering charcoal by gastric tube to rabbits go slowly as their stomach is thin walled and could easily be ruptured. When giving activated charcoal to the avian patient, take into consideration the crop volume.

**Species** | **Crop Volume (ml)**
--- | ---
Finch | 0.1-0.5
Canary | 0.25-0.5
Budgie | 1
Lovebird | 1-4
Cockatiel | 2-4
Small Parrot | 3-6
Medium parrot | 10-15
Large Parrot | 20-30

**Cathartics**
Magnesium sulfate should not be used in reptiles as their slow GI transit time can allow large amounts of magnesium to be absorbed.

**Glue traps**
Use oily substance (mineral oil, cooking oil, etc.) to break down glue. Remove oil with liquid dish washing detergent.

**Toxic vapors**

**Carbon monoxide (CO)**
Carbon monoxide (CO) is produced by inefficient combustion of carbon based fuels (wood, coal, petroleum, natural gas) and is toxic to all species of domestic animals, birds, and humans. CO will accumulate in garages, homes, closed trailers, and livestock housing units. It has a similar density to air, so it does not segregate or stratify readily. CO competes with oxygen for binding to hemoglobin. CO has 240 times the affinity of oxygen for hemoglobin. This higher affinity results in production of carboxyhemoglobin (COHb) over time. Acute CO poisoning results when COHb concentration in blood exceeds 30%. For dogs, 3700 ppm of CO for 1-2 hours produces 70% COHb with apnea and death. Birds (with high respiratory and metabolic rates) are generally more susceptible than mammals. Carboxyhemoglobin is readily detected in blood, and the test is available at many clinical laboratories, in hospitals and some veterinary diagnostic laboratories. Acute CO toxicosis causes rapid depression, coma, respiratory paralysis and death. The blood is bright red due to the inherent color of carboxyhemoglobin. The skin and mucous membranes may be pink. Anoxia causes necrosis of the cerebral cortex and white matter, globus pallidus and brain stem. Recovered animals can have permanent brain damage and locomotor impairment. COHb is very stable and this may prevent spontaneous recovery to oxyhemoglobin when CO exposure ceases. Hyperbaric oxygen is used in human medicine to drive CO from hemoglobin binding sites. If hyperbaric oxygen is available, it is the treatment of choice for our patients. If not available, place the animal in an oxygen rich environment until able to intubate and ventilate as needed with 100% oxygen. Carbon monoxide prognosis is guarded unless hyperbaric oxygen is available. Poisonings can be prevented in homes and animal confinement units with alarmed CO detectors.
Polytetrafluoroethylene (PTFE, Teflon®)

Although polytetrafluoroethylene (PTFE, Teflon®) is inert under ordinary circumstances, when the polymer is heated under conditions of inadequate ventilation, PTFE fumes may result. Small pet birds are extremely sensitive to chlorofluorocarbon fumes, which sensitize the myocardium causing arrhythmias, pulmonary congestion and cardiac failure. With PTFE toxicosis, birds will show respiratory signs immediately. Most die quickly, but some may survive and die later. Environmental conditions and ventilation can be vastly different between rooms and homes. Birds that die may not be in the closest rooms to the PTFE source.

<table>
<thead>
<tr>
<th>Temperature (F)</th>
<th>Common Cooking Temperatures</th>
</tr>
</thead>
<tbody>
<tr>
<td>325</td>
<td>Birds died from preheated oven (Stewart, 2003)</td>
</tr>
<tr>
<td>350</td>
<td>Common baking temperature</td>
</tr>
<tr>
<td>396</td>
<td>Temperature of PTFE-coated light bulbs under which Missouri birds died (Boucher, 2000)</td>
</tr>
<tr>
<td>500</td>
<td>Searing temp for meat in oven or grill</td>
</tr>
<tr>
<td>536</td>
<td>Birds killed in DuPont lab experiments</td>
</tr>
<tr>
<td>700</td>
<td>Preheated grill</td>
</tr>
<tr>
<td>750</td>
<td>Surface of PTFE-coated pan after heating for 8 minutes on conventional stove (Wells, 1982)</td>
</tr>
<tr>
<td>1000</td>
<td>Drip pans (gas range)</td>
</tr>
<tr>
<td>1500</td>
<td>Broiling temperature for high-end ovens</td>
</tr>
</tbody>
</table>

Smoke

Smoke can be generated by the burning of many different substances. With smoke inhalation, dyspnea may be delayed several hours. Treatment is oxygen, bronchodilators and possibly diuretics.

Other vapors

<table>
<thead>
<tr>
<th>Substance</th>
<th>Where Found</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>Paints, solvents, cleaning agents</td>
<td>CNS depression, narcosis, respiratory irritation. Excreted in expired air. Possible inhalation pneumonia.</td>
</tr>
<tr>
<td>Benzene</td>
<td>Paint and varnish removers</td>
<td>Respiratory and dermal irritation; CNS depression; prolonged exposure may cause blood dyscrasia</td>
</tr>
<tr>
<td>Heptane</td>
<td>Waterproofing agents</td>
<td>Dyspnea, pulmonary edema</td>
</tr>
<tr>
<td>Mineral spirits</td>
<td>Painting and refinishing solvents</td>
<td>Dermal and GI irritation. Less volatile than toluene, xylene or naphtha</td>
</tr>
<tr>
<td>Painter's naphtha</td>
<td>Solvent for lacquers and fast drying paints</td>
<td>CNS depression, ataxia.</td>
</tr>
<tr>
<td>Toluene</td>
<td>Anthelmintics, inks, dyes, varnishes, paints, adhesives</td>
<td>Ataxia, depression; cerebellar, liver and renal damage.</td>
</tr>
<tr>
<td>Xylene</td>
<td>Thinners, rubber solvents, adhesives, lacquers</td>
<td>Ocular and dermal irritation, impaired vision, tremors, salivation, coma.</td>
</tr>
</tbody>
</table>

Other household items with strong fragrances or odors can all cause respiratory irritation in our small mammal and avian patients. Treatment for most of the animals is insuring good ventilation. Remove to fresh air and supply oxygen if needed. Remind owners to remove animals before using such products.

Heavy metals

Lead

Lead toxicosis, termed “plumbism,” has been recognized in both humans and domestic animals for thousands of years. All species of animals are susceptible to lead toxicosis, but it has been most commonly associated with waterfowl. Wildlife may still be exposed to lead from lead shot deposited prior to the ban or used to hunt upland game, from ingestion of lead sinkers or jigs lost by fishermen, from environmental contamination from lead smelters or sewage sludge, or from ingestion of tissue from prey containing lead shot or bullets. Captive wildlife and household pets may ingest lead from leaded paints or caulking in old facilities or on old machinery/equipment, from some galvanized containers, or from linoleum, any of which may unknowingly be present in their enclosures. Lead interferes with a variety of metabolic activities within the body, including red blood cell production, bone formation, nerve transmission, and immune function. Anemia and immunosuppression are common features of chronic lead toxicosis in humans and animals. Competition with calcium in the body results in lead being stored in the bone and also leads to alterations of nerve and muscle function. Interference with cell membrane-associated pumps results in cellular damage in the kidney, liver and myocardium. Lead may also cause reproductive dysfunction in a variety of species.

The clinical signs of lead toxicosis will vary depending on whether the exposure is acute or chronic, and death may occur within a few days to several months depending on the degree of exposure (e.g. number of shot ingested). Acute lead toxicosis in mammals generally produces signs of gastrointestinal and CNS dysfunction. Affected mammals may develop anorexia, vomiting, diarrhea, lethargy, behavior disorders, hyperesthesia, ataxia, blindness, seizures, paralysis, coma and death. Avians develop an impacted crop.

Treatment of lead toxicosis includes eliminating the metal from the gastrointestinal tract, chelation therapy to reduce blood lead levels, and general supportive care. Animals showing severe clinical signs should be stabilized as needed prior to institution of other therapies. Removal of lead objects from the gastrointestinal tract is necessary prior to attempts at chelation, as most chelators will

668
enhance lead absorption from the gastrointestinal tract and thereby increase blood lead levels if there is lead in the gut. Calcium EDTA, penicillamine and succimer (DSMA) can be used a chelators.

**Zinc**

Zinc is an essential mineral. Most commonly, animals are exposed through ingestion of zinc from objects such as carpentry hardware (e.g. nuts and bolts), US pennies, and galvanized containers. Zinc-containing objects in the stomach or gizzard are slowly corroded by the low pH, releasing zinc that is readily absorbed into the bloodstream. Zinc is directly damaging to red blood cells, resulting in hemolysis. Renal failure secondary to the hemolysis may develop. Because zinc is irritating to the gastrointestinal tract, vomiting may be noted for a few days prior to the onset of more severe signs. Animals may subsequently present with weakness, lethargy, pallor, ataxia and collapse. Radiographic identification of metallic foreign bodies in the stomach or gizzard may help in determining if zinc toxicity is possible. Bloodwork should be evaluated for evidence of anemia, hemoglobinemia, hemoglobinuria, and/or icterus. Serum zinc levels can aid in diagnosis, but turnaround times may be too long. Zinc levels over 200 ug/dl are considered diagnostic. Treatment of zinc toxicosis entails stabilizing the patient (blood transfusions, etc.) and removal of any metal from the gastrointestinal tract.

**Pesticides**

**Anticoagulant rodenticides**

The injectable Vitamin K1 can be given orally in our patients too small for the oral capsules/tablets.

**Pyrethrins**

Pyrethrin based sprays can cause seizures in snakes. Fish are also very sensitive to pyrethrins and they should not be used around fish tanks or ponds where run off could be a problem.

**OP/carbamates**

Reptile exposure to OPs or carbamates can cause signs similar to mammals: salivation, ataxia, muscle fasciculation, inability to right themselves, coma, respiratory arrest, seizures and death. Birds are also very sensitive to organophosphates. Treatment of OP/carbamate toxicity as also similar to mammals.

**Ivermectin**

Ivermectin cannot be used by injection in any of the chelonian species. The use of this medication will result in flaccid paresis or paralysis. Some lizards and snakes (ball pythons) may also show mild neurologic signs when treated. Prognosis for turtles/tortoises is poor.

**Fipronil (Frontline®)**

Seizures have been seen in rabbits a few hours up to 4-5 days post fipronil exposure. The mechanism of action is unknown. Once seizures begin prognosis is guarded.

**D-limonene**

D-limonene is found in citrus oil flea dips and is toxic to male rats. D-limonene causes renal failure in these animals by binding to α2u-globulins leading to protein accumulation in the renal tubules.

**Medications**

**NSAIDs**

Ferrets are the most likely exotic species to get into human medications. An acute ibuprofen overdose in ferrets is associated with GI, renal, and CNS (coma). Treatment is the same as for other species.

**Acetaminophen**

Ferrets have low levels of acetaminophen UDP-glucuronosyltransferase activity; only the cat has lower levels. Due to the ferret’s inability to detoxify acetaminophen, they should be decontaminated at the same doses as cats and treated the same.

**Venlafaxine**

Venlafaxine (Effexor®) is an antidepressant. Ferrets are attracted to the taste of this medication. Mydriasis, vomiting, tachypnea, tachycardia, ataxia and agitation are the most common signs. Acepromazine may be used for the agitation, and cyproheptadine may be useful in antagonizing the serotonin effects.

**Plants**

**Cardiac glycosides**

Oleander (Nerium oleander), foxglove (Digitalis purpura), Lilly of the valley (Convallaria majalis), dogbane (Apocynum sp.) and squill (Scilla [Urginea] maritima) all contain cardiac glycosides. The cardiac glycosides act like digoxin. The general symptoms of cardiac glycoside poisoning include diarrhea, abdominal pain, irregular pulse, tremors, and convulsions. In severe cases, death occurs. Some of our exotic patients do not have the same progression of signs. Rabbits, rodents (except the prairie dog), and reptiles did not have any GI signs, they went straight into heart failure. Treatment is supportive care, and Digibind® (Digoxin specific FAB fragments) may be used if arrhythmias are non-responsive to traditional medications.
Avocados have been associated with toxicity. They cause sterile mastitis in mice, goats and other livestock and myocardial necrosis in birds and horses. Death occurs 24-47 hours post exposure.

**Insoluble calcium oxalate plants**

Plants of the Araceae family are a common cause of plant poisoning. They include dumbcane (*Dieffenbachia* sp), philodendron, elephant ear (*Alocacia antiquorum*), caladium, and Jack-in-the-pulpit (*Arisaema* sp). The plants contain calcium oxalate crystals which irritate mucous membranes and cause histamine release. Clinical signs may include oral pain and irritation, hypersalivation, head shaking, dyspnea, nausea, vomiting, and diarrhea. Treatment includes rinsing the mouth with milk to help precipitate the oxalates.

**Mycotoxins**

**Aflatoxins**

Avians are more sensitive to aflatoxins than other domesticated species. However, all mammals are susceptible. Aflatoxins are usually associated with cereal grains, corn and peanuts. Clinical signs include lethargy, weight loss, anorexia, ataxia, regurgitation and polydipsia. Long term ingestion can lead to liver cancer.

**Other**

**Lucibufagins (fireflies)**

Lizard deaths have been reported as happening after consumption of fireflies. Researchers have identified chemicals in fireflies that are related to their luminescence. Some of these chemicals are similar to digitalis.

**Avian botulism**

Avian botulism is a paralytic, often fatal, disease of birds resulting from ingestion of toxin produced by *Clostridium botulinum*. There are seven types of toxins (A-through G). Waterfowl die-off is usually from type C; sporadic die off among fish-eating birds (common loons, gulls) from type E toxin, and domestic chickens can be affected by type A. *C. botulinum* spores persist in the soil for years. Toxin production occurs during multiplication of the vegetative form when conditions are favorable (dead organic matter, lack of oxygen, temperature 75 F, pH 5.7-6.2, water depth). The toxin production takes place in decaying animal carcasses. Maggots concentrate toxin and the waterfowl eats the now poisonous maggots. Death of the waterfowl then perpetuates the cycle. The toxin affects peripheral nerves and results in paralysis of voluntary muscles and inability to fly and paralysis of leg muscles (early sign). Paralysis of the nictitating membranes and neck muscles follow. Death is from drowning or from respiratory failure. Prompt removal and proper disposal of carcasses is key in controlling the disease. Providing supportive care and antitoxin injections may provide 75-90% recovery rate (high cost).

**Chlorine**

The use of chlorinated tap water without pretreatment with dechlorinating agents can create lethal chlorine levels which can kill all fish in the tank/pond within hours. Dechlorinators placed after the fact and water changes may help decrease mortality.