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Newer Antidotal Therapies

Charlotte Means
DVM, MLIS, DABVT, DABT

INTRODUCTION

A perfect antidote would be inexpensive, readily, and widely available, able to be administered orally, 100% effective, have no side effects, be labeled for use in all small animal species, and treat a wide variety of toxicants. Unfortunately, there is no such thing as a perfect antidote. The expense, side effects, and availability all need to be considered when deciding on whether to administer an antidote.

Unless the antidote has immediate, life-saving properties, stabilizing the patient and providing supportive care should take precedence over administering the antidote. For example, using atropine in an animal with respiratory rales that was exposed to an organophosphate is immediately antidotal by drying up the bronchial secretions and preventing death due to asphyxiation and should precede any other care.

TYPES OF ANTIDOTES

A single antidote can fall into different categories, depending on the toxicant it is supposed to be counteracting.

Chemical Antidotes

Chemical antidotes will act directly on the toxicant to directly make it less toxic and/or to increase the excretion. For example, calcium disodium EDTA allows lead to displace the calcium in the complex and then forms a water-soluble complex that can be excreted in urine.

Pharmacological Antidotes

Pharmacological antidotes antagonize the toxicant at the receptor site by either binding the toxicant or binding to the target of the toxicant. For example, atipamezole is an alpha2-adrenergic antagonist that can be used to reverse alpha2-adrenergic agonists by working at the receptor site.

Functional Antidotes

Functional antidotes counteract the clinical signs caused by the toxicants. For example, methocarbamol is a centrally acting muscle relaxant that functionally counteracts the tremors caused by strychnine intoxication.

CHELATORS

The perfect chelator would be water soluble, resistant to biotransformation, able to reach the sites of metal storage, would form nontoxic complexes that would be excreted from the body, and would have a low affinity for essential metals. However, like the perfect antidote, the perfect chelator doesn't exist.

Calcium Disodium EDTA

Calcium disodium EDTA allows heavy metals to displace the calcium and then forms a water-soluble complex that can be excreted in urine. It is commonly used to chelate lead and zinc. It will also chelate cadmium, copper, cobalt, iron, nickel, chromium, manganese, plutonium, thorium, uranium, yttrium, and vanadium. It will chelate essential minerals, so supplementation of zinc (if not treating for zinc toxicity) and iron is recommended during the course of treatment. Treatment for lead intoxication with calcium disodium EDTA will initially increase plasma levels of lead, and may cause worsening of clinical signs. Calcium disodium EDTA is nephrotoxic and should only be used on well-hydrated patients. Do not use sodium EDTA, as it will readily bind to blood calcium and cause fatal hypocalcemia.

Dimercaprol

Dimercaprol (BAL, British anti-Lewisite) was developed during World War II as an antidote to Lewisite. It is not soluble in water, so it is dissolved in peanut oil. The intramuscular injections are extremely painful. Dimercaprol is used to chelate arsenic and occasionally lead or mercury. Dimercaprol will donate a sulfhydryl group to chelate a variety of heavy metals, such as lead, arsenic, inorganic mercury, antimony, bismuth, chromium, nickel, copper, zinc, and tungsten. Dimercaprol can remove lead from the brain and central neurologic system (CNS) tissue and is recommended in cases of lead intoxication that are showing severe CNS signs. Do not use with iron, cadmium, or selenium toxicity as the chelated products are more toxic than the metals alone.

Succimer

Succimer (2, 3 dimercaptosuccinic acid, DMSA) is often used for chelation in pediatric cases with lead toxicosis. Succimer can be used to chelate lead, arsenic, and mercury. Succimer has several advantages over dimercaprol: it is administered orally, is less nephrotoxic, is less upsetting to the gastrointestinal tract, and is less likely to cause zinc, iron, calcium, or magnesium deficiency. Unlike many other oral chelators, succimer does not increase the absorption of target metals from the gastrointestinal tract, so it can be given at any time, even if the gastrointestinal tract is not free of metal. However, succimer is also more expensive than most of the other chelators. It is not uncommon to see a post-chelation increase in blood lead levels due to redistribution of lead from bone and tissue stores. If lead levels are still increased and the patient is symptomatic, succimer should be redosed. If they are asymptomatic, there is no need to retreat.

Deferoxamine

Deferoxamine (Desferal) is used in humans to treat acute iron toxicosis and chronic iron and aluminum overload. Deferoxamine is used in animals for both chronic and acute iron toxicity. The urine will turn pink to orange red (vin rosé) while the chelated iron is being excreted. Deferoxamine is typically given intramuscularly, as intravenous injections can cause hypotension and pulmonary edema. Total iron binding capacity (TIBC) and serum iron (SI) levels are not reliable during chelation therapy; therefore, the endpoint used is typically clear yellow urine and resolution of clinical signs associated with iron intoxication.

IMMUNOTOXICOTHERAPY

Commercial Antibodies

Commercial antibodies are antitoxin-specific serum or monoclonal antibodies. The dosing depends on the serum plasma concentrations of the toxin and not the body weight of the patient. They decrease the free form of the toxin, tissue concentrations and increase elimination.

Digoxin Immune Fab

Digoxin immune Fab fragments are antidigoxin antibodies derived from sheep immunized to digoxin. Digoxin immune Fab binds directly to digoxin and inactivates it. Fab fragments have a high affinity for digoxin and can even remove it from the Na^+/K^+ ATPase pump binding site and render it inert. It is indicated for the treatment digoxin toxicosis, bufotoxins from *Bufo* toads, and *Digitalis* glycoside-containing plant toxicosis (see Table 1).

Table 1. Cardiac glycoside-containing plants that may be treated with digoxin immune Fab

Scientific name	Common name
Acokanthera oblongifolia	Poison arrow plant
Adonis microcarpa	Pheasant's eye
Asclepias physocarpa	Balloon cotton bush
Bryophyllum tubiflorum	Mother of millions
Calotropis procera	King's crown
Carissa laxiflora	Bush plum
Cerbera manghas	Sea mango
Convallaria majalis	Lily of the valley
Cryptostegia grandiflora	Rubber vine
Helleborus sp.	Hellebore, Christmas rose, Lenten rose
Nerium oleander	Oleander
Thevetia neriifolia, T. peruviana	Yellow oleander
Urginea maritima	Squill

Digoxin immune Fab is reserved for life-threatening cases with severe ventricular dysrhythmias, progressive bradyarrhythmias, or second- or third-degree atrioventricular heart block that does not respond to treatment. It can reverse severe bradyarrhythmias and tachyarrhythmias that are not responding to conventional therapies.

Urine output should be monitored in cases where digoxin immune Fab is given. The complexes are renally excreted and can dissociate if the animal is not eliminating them, causing recurrence of the clinical signs.

ENZYME INHIBITORS

Enzyme inhibitors are used with substances that become toxic after *in vivo* metabolism. They can decrease the amount of toxic metabolites either through competitive inhibition or reversible inhibition. This gives the animal time to eliminate the parent compound. Enzyme inhibitors need to be given early in the course of the toxicosis before there is significant accumulation of the toxic metabolites.

Ethanol

Ethanol is an inhibitor of alcohol dehydrogenase used to prevent ethylene glycol toxicosis. It has a higher affinity for alcohol dehydrogenase than ethylene glycol and prevents it from metabolizing ethylene glycol into the toxic metabolites that cause acidosis and acute renal failure. Without alcohol dehydrogenase to metabolize ethylene glycol, the ethylene glycol is excreted unchanged in the urine. Because ethanol works by inhibiting the metabolism of ethylene glycol to toxic metabolites, it is most effective with early treatment before ethylene glycol has been metabolized.

Fomepizole

Fomepizole (4-MP, 4-methylpyrazole) is an inhibitor of alcohol dehydrogenase used to prevent ethylene glycol intoxication in small animals. Fomepizole binds to alcohol dehydrogenase and prevents it from metabolizing ethylene glycol into the metabolites that cause acidosis and acute renal failure. Because fomepizole works by inhibiting the metabolism of ethylene glycol to toxic metabolites, it is most effective with early treatment before ethylene glycol has been metabolized. Fomepizole is superior to ethanol for treatment of ethylene glycol intoxication as it does not worsen the depression or acidosis seen from ethylene glycol and does not cause hyperosmolality.

PHARMACOLOGICAL ANTIDOTES

Pharmacologic antidotes can work in several ways: they can bind to the toxin, bind to the target (either preventing the toxin from binding to its target or acting as a receptor agonist when the toxin is an antagonist or vice versa), or reversing the chemical reaction.

RECEPTOR ANTAGONISTS

Receptor antagonists bind to the receptors themselves but do not activate the receptor, thus limiting access to the receptor.

Flumazenil

Flumazenil has a higher affinity for benzodiazepine receptors than benzodiazepines and competitively blocks them at the receptor site. Flumazenil reverses the CNS and respiratory depression caused by benzodiazepines 1–2 minutes post-administration. The half-life is one hour, so repeated doses are often necessary. Flumazenil is contraindicated in patients with tricyclic antidepressant overdoses, as it can cause seizures.

Atipamezole

Atipamezole is an α2-adrenergic antagonist that can be used to reverse α2-adrenergic agonists, such as amitraz, imidazole decongestants, clonidine, tizanidine, and xylazine. Atipamezole is preferred over yohimbine as it is a more specific α2-adrenergic agonist. It will reverse sedation, bradycardia, and hypotension caused by α2-adrenergic agonists.

Cyanide Antidotes

Sodium Nitrite and Sodium Thiosulfate

Sodium nitrite is used to treat cyanide intoxication by inducing low levels of methemoglobinemia. The methemoglobin will remove cyanide bound to cytochrome oxidase and form cyanmethemoglobin. Caution should be used with hypotensive animals as sodium nitrite has been shown to worsen hypotension associated with cyanide intoxication. Animals that survive longer than one hour post-exposure are likely to live. Sodium nitrite can be used in combination with sodium thiosulfate, which supplies sulfur for the rhodanese reaction and produces thiocyanate, which is then excreted in the urine.

Hydroxocobalamin

Hydroxocobalamin is a vitamin B precursor used to treat cyanide. When in the presence of cyanide, hydroxocobalamin binds the cyanide to form cyanocobalamin (vitamin B12), which is then excreted in the urine. It is considered very safe. Hydroxocobalamin is equally effective in preventing mortality when compared to sodium nitrate combined with sodium thiosulfate for treatment of cyanide intoxication. Additionally, hydroxocobalamin can decrease the hypotension indicative of cyanide intoxication, which is thought to occur by a nitric oxide release. Hydroxocobalamin is also a nitric oxide scavenger and is thought to reverse the hypotension caused by the presence of nitric oxide.

Pamidronate

Pamidronate is a bisphosphonate used to treat hypercalcemia by binding to hydroxyapatite in bone and inhibiting the osteoclastic bone resorption of calcium. It has been shown to reverse the hypercalcemia and hyperphosphatemia in dogs exposed to cholecalciferol. Pamidronate lowers calcium within 24–48 hours after administration and is long lasting. It is more expensive than calcitonin, another bisphosphonate, but is often more cost effective, as it is longer lasting. Do not use calcitonin and pamidronate together, as it increases mortality.

Pyridoxine

Vitamin B6 (pyridoxine) is used in the treatment of isoniazid and *Gyromitra* mushroom toxicosis. Isoniazid depletes pyridoxine which is a precursor of GABA. This causes lowered levels of GABA in the CNS and is thought to be the mechanism by which overdoses of isoniazid cause seizures. By supplying additional pyridoxine, this inhibited step is skipped and GABA levels remain normal.

Intravenous Lipid Emulsion

Intravenous lipid emulsion (ILE, intralipids) is used to treat some lipophilic xenobiotic overdoses. The mechanism of action is unknown, but one of the current theories is that it acts as a lipid shuttle. ILE can potentially hasten recovery time, reducing the time needed for intensive care. Xenobiotics that are more successfully treated by ILE are those that are lipophilic and have a high LogP. Current potential medications that ILE has been tried in include ivermectin, moxidectin, calcium channel blockers, baclofen, local anesthetics (such as lidocaine and bupivacaine), permethrin, lamotrigine, and antidepressants. Potential complications with ILE include hyperlipidemia, pancreatitis, transient increased liver enzymes, volume overload, fat overload syndrome, and removal of other medications and antidotes used for treatment of the toxicosis. ILE is relatively safe, inexpensive, and often readily available.

Cyproheptadine

Cyproheptadine is used as an antihistamine, an appetite stimulant, and a serotonin antagonist. Serotonin syndrome is associated with ingestion of drugs that increase brain serotonin levels, such as selective serotonin reuptake inhibitors, amphetamines, 5-hydroxytryptophane, etc. Cyproheptadine can be used to help treat serotonin syndrome.

N-acetylcysteine

N-acetylcysteine (NAC) is used as a mucolytic agent and in the treatment of acetaminophen toxicosis. Acetylcysteine is a precursor of glutathione synthesis and can also be oxidized to provide organic sulfate needed to metabolize APAP through the sulfation pathway. It also provides an alternate substrate for conjugation to reduce the extent of liver injury or methemoglobinemia.

Dantrolene

Dantrolene is used in the prevention and treatment of malignant hyperthermia syndrome and the malignant hyperthermia-like syndrome associated with the ingestion of hops (*Humulus lupulus*) in dogs.

Cholestyramine

Cholestyramine is an anion exchange resin. Originally, it was used to treat hypercholesterolemia in humans. Now, it is also used in the treatment of toxicoses in humans with agents that undergo enterohepatic recirculation, such as amiodarone, digoxin, chlordane, methotrexate, piroxicam, cholecalciferol, warfarin, blue green algae, and indomethacin. Cholestyramine binds with bile acids in the intestine and prevents them from being reabsorbed, stopping enterohepatic recirculation. Cholestyramine is a powder that is given before feeding or mixed with canned food. Patient compliance can be an issue as it is typically citrus flavored.

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