Five minutes before your clinic closes, a dog arrives laterally recumbent, unresponsive, and profoundly hypoglycemic. The differential diagnoses that run through your mind include insulinoma, hypoadrenocorticism, liver disease, and sepsis, among many others. When reviewing the DAMNITV differential diagnosis scheme (Degenerative, Anomalous, Metabolic, Neoplastic or Nutritional, Inflammatory, Traumatic or Toxic, Vascular), you focus on the “T” (for toxic) and think of numerous substances that can cause hypoglycemia. However, most of them may be encountered only rarely or occur only theoretically. This article is intended to help you rule out the rare causes and focus on those that should be on your short list: the top 10. After you have stabilized the patient, discussing these substances with the client may help pinpoint the cause of hypoglycemia.

We start with the least likely and work our way to the most likely.

10. BACLOFEN

Description: Baclofen is a centrally acting skeletal muscle relaxant.

Clinical signs: Ingestion of baclofen may cause vomiting, hypersalivation, agitation, ataxia, vocalization, mydriasis, depression, recumbency,
hypothermia, hypotension or hypertension, tremors, seizures, coma, and respiratory arrest.

**Margin of safety:** Narrow. The therapeutic dose for dogs has been listed as 1 to 2 mg/kg PO q8h.\(^1\) However, clinical signs, such as ataxia and recumbency, have occurred after receipt of 0.5 mg/kg. Seizures, loss of gag reflex, and coma have occurred after receipt of 1 to 2 mg/kg.\(^2\)

**Mechanism for hypoglycemia:** Direct and indirect. The exact mechanism is unknown, but hypoglycemia may result from suppression of glucagon release.\(^3\) In dogs with severe tremor or seizure activity, increased use of glucose could lead to hypoglycemia.

**Treatment Tip** Be ready to intubate. Dogs often lose their gag reflex early in the course of intoxication and need respiratory support. Baclofen can cause flaccid paralysis of the diaphragm.\(^4\)

### 9. METALDEHYDE

**Description:** Metaldehyde is a common active ingredient in molluscicides.

**Clinical signs:** Ingestion of metaldehyde most often results in seizures, hypersalivation, vomiting, diarrhea, hyperesthesia, tremors, twitching, ataxia, hyperthermia, tachycardia, nystagmus, acidosis, cyanosis, and death.\(^5\) Liver failure may also occur 2 to 3 days later.\(^2\)

**Margin of safety:** Narrow. Any exposure is cause for concern.

**Mechanism for hypoglycemia:** Direct and indirect. Severe muscle activity can lead to hypoglycemia from increased metabolic use of glucose. Liver failure can also cause hypoglycemia.

**Treatment Tip** Metaldehyde exposure is anecdotally described as a “shake and bake” toxic syndrome, and its treatment typically requires methocarbamol and benzodiazepines to control tremors. Hyperthermia, rhabdomyolysis, acidosis, and disseminated intravascular coagulation can result.

### 8. METHYLMXANTHINES

**Description:** Methylxanthines include caffeine, theobromine, and theophylline. This broad category encompasses chocolate, diet pills, caffeinated beverages, bronchodilators (e.g., aminophylline, theophylline), and more.

**Clinical signs:** Methylxanthine toxicosis can cause panting, pacing, restlessness, tachycardia, hypertension, hyperthermia, arrhythmias, tremors, and seizures. Vomiting, diarrhea, polyuria, and polydipsia are also common.

**Margin of safety:** Variable. The margin of safety for chocolate is wide, depending on the type of chocolate (TABLE 1); the margin of safety for medications such as theophylline is narrower.

**Mechanism for hypoglycemia:** Direct and indirect. Methylxanthines may cause increased insulin release and insulin sensitivity.\(^6\) In severely affected dogs, hypoglycemia may result from increased metabolic use of glucose.

**Treatment Tip** Dogs that have ingested large amounts of chocolate are often hemoconcentrated. The osmotically active environment puts them at high risk for hypernatremia or other electrolyte imbalances. For this reason, activated charcoal should be used with caution. It is not needed in all dogs that have ingested chocolate.

### 7. SAGO PALM

**Description:** Sago palms are decorative plants commonly found outdoors in warm climates, but they can be kept indoors in any region. They are also known as cycads. The genera of concern are *Microzamia*, *Zamia*, and *Cycas*.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>METHYLMXANTHINE CONCENTRATION, MG/OZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>White chocolate</td>
<td>1.1</td>
</tr>
<tr>
<td>Milk chocolate</td>
<td>65</td>
</tr>
<tr>
<td>Dark/semisweet chocolate</td>
<td>165</td>
</tr>
<tr>
<td>Baker’s chocolate (unsweetened)</td>
<td>400</td>
</tr>
<tr>
<td>Dry cocoa powder</td>
<td>790</td>
</tr>
</tbody>
</table>

TABLE 1 Average Methylxanthine Concentration of Chocolates
Clinical signs: Sago palm toxicosis can cause vomiting and diarrhea (with or without blood), lethargy, depression, dehydration, anorexia, ascites, abdominal pain, icterus, tremors, ataxia, seizures, coma, and death. Liver failure, coagulopathies, and thrombocytopenia may also be seen, but their onset may be delayed by 2 to 3 days.

Margin of safety: Narrow. All parts of the plant are toxic, but the most toxic parts are the seeds. Any exposure is a concern.

Mechanism for hypoglycemia: Direct and indirect. The toxins decrease the activity of mitochondria, adenosine triphosphate, and glucose-6-phosphatase, thereby decreasing gluconeogenesis and glycogenolysis. Hypoglycemia may also be associated with liver failure and/or sepsis.

Treatment Tip: The key action to take is aggressive decontamination. For dogs brought to you early, while still asymptomatic, the best course of action is inducing emesis, followed by giving multiple doses of activated charcoal. Cholestyramine may also be used in some cases to decrease enterohepatic recirculation. Cholestyramine is a powdered bile acid sequestrant that is widely available at human pharmacies. It binds bile and, by default, the toxins already bound to the bile. Cholestyramine should be given with food and also aids in elimination of cholecalciferol, amatoxin, and some nonsteroidal anti-inflammatory drugs (NSAIDs) (see numbers 3 and 4 below).

6. ZINC AND ALUMINUM PHOSPHIDE

Description: Zinc phosphide is an agent commonly used for mole and gopher control; aluminum phosphide is used to fumigate grain stores for insect and rodent control. Clinical signs can develop from inhalation of aluminum phosphide. After ingestion of zinc phosphide bait, phosphine gas is released when the product is exposed to the acidic environment of the stomach. The phosphine gas is rapidly absorbed via inhalation during eructation or across the gastric mucosa. The hydrolyzed phosphine causes significant oxidative damage throughout the body. Zinc toxicosis is not expected.

Clinical signs: Zinc or aluminum phosphide exposures cause vomiting, hypersalivation, tremors, respiratory distress, ataxia, weakness, hyperesthesia, and seizures and, in some cases, may progress quickly to death. It is common for patients to have a strong odor to their breath, often described as a pungent garlic smell. Neurologic signs can develop soon after ingestion. Liver and kidney damage may occur days to weeks after ingestion.

Margin of safety: Narrow. Any exposure has the potential to cause clinical signs.

Mechanism for hypoglycemia: Direct and indirect. Impairment of glycogenolysis and gluconeogenesis can lead to hypoglycemia. Adrenal gland injury and low levels of cortisol may also play a role. Animals experiencing severe seizure activity may become hypoglycemic because of increased metabolic use of glucose.

Treatment Tips
- As soon as possible, administer 1 tablespoon of aluminum hydroxide or magnesium hydroxide per 20 pounds of body weight. Doing so will increase the pH of the stomach and decrease the amount of phosphine gas released. If possible, avoid inducing emesis with hydrogen peroxide; ideally, emesis should be induced with apomorphine while the animal is outdoors.
- Phosphine gas is toxic to all living creatures. Clients should drive to the clinic with the windows down, in case the dog vomits in the car. Any questions regarding humans (clients and/or veterinary hospital employees) who may have been exposed to phosphine gas should be immediately directed to Human Poison Control (1-800-222-1222).

5. SYMPATHOMIMETICS

Description: Sympathomimetics directly or indirectly cause an increase in catecholamines at the neuronal junction. Examples of sympathomimetics include amphetamines, prescription medications for attention-deficit/hyperactivity disorder or attention-deficit disorder, phenylpropanolamine, decongestants (e.g., pseudoephedrine), and illicit drugs (e.g., cocaine, crystal methamphetamine, and 3, 4-methylenedioxymethamphetamine [MDMA, ecstasy]).

Clinical signs: Sympathomimetics can cause agitation, aggression, ataxia, tachycardia or bradycardia, hypertension, hyperthermia, vocalization, mydriasis, tremors, and seizures.
Margin of safety: Variable, depending on the substance.

Mechanism for hypoglycemia: Direct and indirect. Hypoglycemia may result from increased use of glucose\(^14\) and possibly increased release of insulin.\(^15\)

Treatment Tip Treatment with acepromazine is very effective because of its \(\alpha\)-adrenergic and dopaminergic-blocking effects.\(^16\) Cyproheptadine may be used in conjunction with acepromazine if signs of serotonin syndrome (e.g., mydriasis, vocalization, hyperthermia, hyperesthesia, agitation, tachycardia, or fasciculation) are seen.

4. NSAIDs

Description: Therapeutic doses of veterinary use approved NSAIDs (e.g., carprofen or deracoxib) or low doses of human use–labeled NSAIDs (e.g., ibuprofen or celecoxib) are not expected to cause hypoglycemia in dogs. However, it is possible to see hypoglycemia with large overdoses of NSAIDs. Ibuprofen accounts for almost half of the documented cases of NSAID-associated hypoglycemia at the Animal Poison Control Center.\(^2\) These cases may be overrepresented because of the popularity of ibuprofen.

Clinical signs: Overdoses of NSAIDs can lead to ulceration of the gastrointestinal tract and renal damage. Clinical signs may include vomiting, diarrhea, depression, melena, hematemesis, polydipsia, and polyuria. Ingestion of more than 350 mg/kg of ibuprofen can lead to neurologic signs, such as ataxia, tremors, seizures, and coma.

Margin of safety: Variable. Most dogs that demonstrate signs of ibuprofen toxicosis with hypoglycemia had ingested more than 350 mg/kg.\(^2\)

Mechanism for hypoglycemia: Direct and indirect. NSAIDs are thought to cause hypoglycemia because of their effect on pancreatic \(\beta\) cells, causing increased insulin secretion.\(^16\) Increased metabolic use of glucose (seizure activity) can lead to hypoglycemia.

Treatment Tip Naloxone may help reverse ibuprofen-induced central nervous system depression or coma.\(^17\)
3. MUSHROOMS WITH AMATOXINS

Description: Most mushrooms ingested by dogs are never identified; the suspected diagnosis is often made from the clinical picture and history. Mushrooms most likely to cause hypoglycemia are those that contain amatoxins (e.g., Amanita phalloides [death cap], Amanita verna [spring destroying angel], Galerina autumnalis [deadly galerna], and Lepiota josenandii [deadly parasol]). The toxic components of these mushrooms consist of amatoxins, phallo toxins, and virotoxins.18

Clinical signs: Death cap mushrooms are among the most widely studied. Exposure to a death cap mushroom can cause clinical signs that occur in 3 phases:

1. Phase 1 includes moderate to severe gastrointestinal signs, tachycardia, fever, and hyperglycemia lasting 24 hours.

2. Phase 2 is a latent phase and may last as long as 24 hours.

3. Phase 3 includes clinical signs such as hypoglycemia, liver and renal failure, coagulopathy, cerebral edema, acidosis, encephalopathy, coma, sepsis, and death.18

Margin of safety: Very narrow. Any exposure is a concern.

Mechanism for hypoglycemia: Direct and indirect. Severe hypoglycemia can occur, presumably resulting from the breakdown of glycogen in the liver.19 In addition, insulin release may result from a cytotoxic effect on β cells.20 Hypoglycemia can also result from liver failure.

Treatment Tip Early and aggressive decontamination is imperative (see Treatment Tip for Sago palm).
2. ANTIHYPERGLYCEMICS

Description: This heading encompasses all oral antihyperglycemic medications and insulin injections. The most common oral antihyperglycemic medications for which the Animal Poison Control Center receives calls are the sulfonylureas (e.g., glipizide and glyburide). The hypoglycemia caused by insulin injections is dose-dependent.

Clinical signs: Aside from hypoglycemia, the clinical signs vary according to the agent.

Margin of safety: Variable. The margin of safety for sulfonylureas and insulin injections is narrow. For others, such as metformin or acarbose, the margin is much wider.

Mechanism for hypoglycemia: The mechanisms vary according to the drug. Sulfonylureas, for example, affect potassium channels on pancreatic β cells, thereby causing release of insulin.

Treatment Tips
- Hypoglycemia with sulfonylurea exposures can be profound, and any exposure is a concern. The hypoglycemic effects can persist for well over 24 hours and after large overdoses may last 72 hours.
- Oral exposure to insulin does not cause hypoglycemia. The insulin is digested in the stomach and is inactivated.

1. XYLITOL

Description: This sugar alcohol is used as a sweetening agent in many foods, candies, mints, chewing gums, and supplements. It is also used as a cooling agent in nasal sprays, diapers, baby wipes, sunscreen, toothpaste, and mouthwashes. Although there are many other sugar alcohols, xylitol is the only sugar alcohol that poses a concern for animal safety.

Clinical signs: Ingestion of xylitol can cause vomiting, depression, diarrhea, hypoglycemia, increased liver enzymes, ataxia, tremors, and seizures. Other signs include liver failure, hepatic encephalopathy, and coagulopathy. Liver failure has been seen within 12 hours but can be delayed up to 72 hours.

Margin of safety: Narrow. Ingestion of 100 mg/kg or more can cause hypoglycemia.

Mechanism for hypoglycemia: Direct and indirect. Xylitol-induced hypoglycemia can be profound and results from insulin release. However, in some animals, liver injury can occur without the hypoglycemic phase. Hypoglycemia can result from liver failure rather than insulin release.

Treatment Tip: Xylitol is poorly absorbed by activated charcoal, and charcoal use for xylitol toxicity is not indicated.

CONCLUSION

This list of toxicologic causes of hypoglycemia in the dog can be a useful tool for the small animal veterinarian. Reviewing these substances with the client may prove to be a practical way to determine the cause of hypoglycemia. Although this list of hypoglycemic substances is not comprehensive, it covers the 10 most common toxicologic causes of hypoglycemia in the dog as reported to the ASPCA Animal Poison Control Center. More information can be found by calling the ASPCA Animal Poison Control Center at 1-888-426-4435 and visiting the ASPCAPro website (aspcapro.org) for helpful printouts, articles, and newsletters.


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Ginger Watts Brown completed a Bachelor of Science in Animal Science and a Doctor of Veterinary Medicine at the University of Illinois in Urbana. After graduating in 2004, she practiced small animal general medicine in New Jersey for 11 years. She began her career with the ASPCA Animal Poison Control in 2015 to pursue her interest in toxicology. In addition to providing phone consultations to veterinary professionals, Dr. Watts Brown is part of the management team at the APCC. She also enjoys writing podcasts and contributing to educational materials for staff and pet owner education.

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